EXHIBIT G

EXPOSURE TO POLYCHLORINATED BIPHENYLS AND NEURODEVELOPMENTAL MEASURES IN CHILDREN

Expert Report

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November 15, 2019

CONTENTS

INTRODUCTION AND SUMMARY OF OPINIONS

I, Michael Goodman, am a Professor in the Department of Epidemiology of the Emory University School of Public Health in Atlanta, GA. I hold two graduate degrees: a Doctor of Medicine (MD) degree from the Kaunas Medical University in my native Lithuania and a Master of Public Health (MPH) degree from the Johns Hopkins University in Baltimore, Maryland. I am a licensed physician with formal training in two disciplines: Pediatrics and Preventive Medicine.

My areas of scientific research include epidemiology of non-communicable diseases, clinical and preventive medicine, and children's health. Over the last 20 years I have worked on a number of clinical and epidemiologic projects sponsored by the United States and foreign governments, industry, and non-profit foundations. I have experience in all major aspects of epidemiologic research including design, implementation, and data analysis of studies of different types.

In addition to conducting original research, I am experienced in systematic literature reviews. Among 229 articles listed in my current curriculum vitae, at least 25 papers can be categorized as systematic reviews.

I have many years of experience in teaching courses in epidemiologic methods and in systematic reviews of the literature. I have taught these subjects as full-semester and short courses in a variety of settings including Emory University, the National Institutes of Health, and the Centers for Disease Control and Prevention.

I was asked to systematically evaluate the epidemiologic evidence and provide an opinion on the presence or absence of an association between exposures to polychlorinated biphenyls (PCBs), at levels typically found in the environment, and various neurodevelopmental measures in children. I was also asked to review the Expert Report of James R. Olson, PhD and evaluate the validity of the opinions related to children's health covered in the sections "Neurodevelopment", "Behavioral Problems, including ADHD and Autism' and "Auditory Function." Based on my review of the above materials I have concluded the following:

1. Despite hundreds of various exposures and neurodevelopmental neurologic and behavioral measures examined across 35 different populations, the existing body of literature does not report any consistent associations between PCBs and neurodevelopmental function in children.

2. The data across and within studies represent a mixture of results in either direction with the majority of findings indicating no significant association.

3. There is no evidence that in populations with higher background PCB exposure levels, the association with neurodevelopmental test results is stronger or more commonly observed compared to populations with lower exposures

4. Studies of specific neurobehavioral and neurodevelopmental diagnoses such as attention deficit hyperactivity disorder and autism spectrum disorder do not support the proposition that incidence of these conditions is related to PCB exposures.

5. Taken together, these observations are reassuring as they offer evidence against a causal relationship between PCBs and neurodevelopmental problems in the general population of children.

6. Dr. Olson's opinion that "PCBs cause an increased risk" of neurobehavioral effects "in general population at background, environmental levels of exposure" is based on highly selective and often erroneous evaluation of the published studies. In arriving at this opinion, Dr. Olson failed to follow the most basic guidelines for conducting a systematic review of the literature.

This report provides the basis for the above opinions, which are held to a reasonable degree of medical and scientific certainty. I will begin the report by introducing some of the epidemiologic concepts and relevant terminology used throughout the text. This is followed by a section that describes the methodology used to evaluate the available evidence, and outlines the specific questions addressed during this evaluation. I will then present my findings with respect to each of the specific questions, synthesize the evidence, and summarize my opinions. In the event any additional information is made available to me in the future, I reserve the right to amend my conclusions accordingly.

OVERVIEW OF EPIDEMIOLOGIC CONCEPTS AND RELEVANT TERMINOLOGY

Definition of epidemiology

Epidemiology is the study of the distribution and determinants of health-related states in populations. Its main role is the determination of disease causation in order to provide information for disease prevention. The scientific and medical communities require supporting epidemiologic studies before they will accept that an agent actually causes a disease in humans.

The purpose of an analytic epidemiologic study is to compare measures of health-related states or conditions in people with different exposures or levels of exposure. This is usually achieved by applying various statistical techniques in which exposure of interest (e.g., an environmental, genetic or lifestyle factor) is called the *independent variable* and the health-related measure is called the *dependent variable*.

The independent and dependent variables can be *continuous*, *ordinal*, or *binary*. For example, study participants can be characterized with respect to their exposure to a chemical or nutrient using blood concentrations of these substances (continuous independent variable), or assigned to low, medium or high exposure categories (ordinal independent variable) or simply divided into two groups – exposed and not exposed (binary independent variable). Similarly, a particular health related measure (e.g., body weight) can be expressed as a number of pounds and ounces (continuous dependent variable), or divided into two or more levels. When the health-related measure under study is a particular clinical diagnosis, it is almost always expressed as a binary variable that describes each participant as having or not having the disease of interest.

Assessment of associations in epidemiology

The association between exposure (independent variable) and health-related measure (dependent variable) can be evaluated in a variety of ways depending on the type of variables used in the analysis. If both the independent and the dependent variables are binary (e.g., smokers vs. nonsmokers and having vs. not having heart disease), epidemiologic studies typically estimate the ratio of the risk of disease in exposed individuals to the risk of disease in unexposed individuals. This ratio is called *relative risk* or *risk ratio*. Depending on the study design relative risk can be estimated using alternative measures such as odds ratio or rate ratio, but the interpretation of these measures is generally the same.

If the relative risk or similar measure equals 1.0, the incidence of disease in the exposed group equals the incidence of disease in the unexposed group and the result is interpreted as "no association." If the relative risk is greater than 1.0, the incidence of disease in the exposed group exceeds the incidence of disease in the unexposed group and the result is interpreted as a positive (not necessarily causal) association. If the relative risk is less than 1.0, the incidence of disease in the exposed group is lower than the incidence of disease in the unexposed group and the result is interpreted as a negative (not necessarily protective) association.

When the health-related measure is expressed as a continuous variable, epidemiologists typically use a *difference*- rather than a *ratio*-based measure of association. For example, if both the

exposure and the dependent variable are continuous, the association between them can be assessed through the use of *correlation or regression coefficients*.

If the coefficient equals 0, the health-related measure does not change regardless of the level of exposure; this is also interpreted as "no association." If the coefficient is greater than 0, the health-related measure on average is higher in people with higher exposure and the result is interpreted as a positive (not necessarily causal) association. If the coefficient is less than 0 (i.e., assumes a negative value) the health-related measure on average is lower in people with higher exposure and the result is interpreted as a negative (not necessarily causal) association.

Both ratio- and difference-based estimates also provide a measure of the magnitude of association. For example, a relative risk of 10 describing the association between lung cancer and smoking means that individuals who smoke have a ten-fold higher incidence of lung cancer in comparison to non-smokers. Similarly, if the regression coefficient reflecting the association between, say, alcohol intake (in grams per day) and systolic blood pressure (in mm Hg) is 0.05 this means that each additional gram of daily alcohol consumption is associated with an average 0.05 mm Hg increase in blood pressure.

Statistical and clinical significance of associations

Even in the absence of any true increase or decrease in risk, rarely do the risk ratio estimates exactly equal 1.0 and similarly even if the exposure is completely unrelated to a particular health measure rarely do the coefficients exactly equal 0. When evaluating an association, epidemiologists always consider the possibility that the detected departure from 1.0 or 0 occurred due to chance.

The likelihood that the observed association could occur due to chance alone is evaluated by using *statistical inference* or tests for *statistical significance*. The tests of statistical significance are usually expressed in two ways: *p-values* and *confidence intervals*.

A p-value determines the probability (likelihood) that the study result, which found an association, would be at least as extreme as observed, if no association truly existed and the result was due to chance alone. The lower the p-value, the less likely it is that the study results are due to chance alone. When the probability of chance (also referred to as *type I error*) is sufficiently low, the result is considered *statistically significant*. Most commonly, the cutoff for statistical significance is a p-value of less than 0.05.

Confidence intervals also provide information about whether or not an association is statistically significant. A confidence interval is a range of values for a parameter of interest (e.g., relative risk or regression coefficient) constructed so that this range has a specified probability of including the true value. A 95% confidence interval is equivalent to a p-value (type I error) of 0.05 and indicates that researchers are 95% confident that the true parameter is between the upper and lower bounds of the confidence interval.

If a relative risk estimate has a 95% confidence interval that includes 1.0, the departure from 1.0 is typically considered statistically non-significant and usually is not accepted as sufficient evidence of a true association. Similarly, if a regression coefficient (or a similar difference-

based measure) has a 95% confidence interval that includes 0, the departure from 0 is typically considered statistically non-significant and usually is not accepted as sufficient evidence of a true association.

When discussing statistical inference, it is important to acknowledge that the tests for significance and the commonly used cutoffs should not replace common sense in interpretation of studies. For example, an association between a particular exposure and disease consistently found in several studies that narrowly missed the conventional cutoff for statistical significance should not be dismissed based on p-values alone. Conversely, it is also important to remember that a statistically significant association may not indicate a clinically or biologically meaningful finding. For example, a very small difference in blood cholesterol observed in a large study may be accompanied by a low p-value; yet this difference may not have any clinical value if it does not confer a higher risk of heart disease.

Association versus causation

The methods discussed above help epidemiologists to evaluate associations between an exposure and a health-related measure. However, the existence of an association does not necessarily imply that the association is causal, that is, that the exposure caused the disease or condition of concern. For example, if a hypothetical study selected participants who were invited to participate because they were known to be exposed and also had the disease of interest, we might observe a false association between exposure and disease due to the flawed study design.

Any systematic error in the study design, implementation or analysis that results in a mistaken measure of association is called *bias*. Identification of bias is critical in conducting and evaluating epidemiologic studies. Several types of bias exist. *Selection bias* refers to systematic differences in the characteristics of those who are selected for study and those who are not. For example, selection bias may invalidate conclusions from surveys that would include only volunteers or persons known to have certain medical conditions. *Misclassification bias* refers to inaccuracies in assigning the "exposed" vs. "unexposed" and "case" vs. "non-case" status. Specific types of misclassification bias include recall bias, interviewer bias, and systematic measurement error.

In addition to selection and misclassification bias, the analysis of an association between two factors can be affected by the presence of a third factor that is unequally distributed among participants. This situation is referred to as *confounding*. A confounder is a factor that distorts the effect of the risk factor under study. For example, an association between alcohol consumption and lung cancer is likely to be false and attributable to the effect of smoking because smoking is related to both alcohol consumption and lung cancer, that is, smoking *confounds* the association between alcohol and lung cancer. If a particular physician usually treats older patients, his or her patients will likely experience higher mortality than those treated by other physicians. In this case, the association between patient mortality and the treating physician is confounded by age.

A mathematical procedure to correct the measures of association in order to eliminate the effect of confounders is called *adjustment*. In drawing their conclusions, epidemiologists typically rely on adjusted estimates. For example, after adjustment for smoking, the risk ratio for coffee

consumption and pancreatic cancer changes from 2.1 to 1.0. Thus, the observed association between pancreatic cancer and coffee consumption is merely due to the fact that people who drink coffee are also more likely to smoke.

In situations where an observed association is not due to a confounder(s) nor is it found to be the result of faulty study design, one needs to determine if this association is causal. This distinction is important from a public health standpoint because we want to know if changing the prevalence of a particular factor in the population will improve the health status of that population.

To cope with the complexity of determining whether a particular association is causal, epidemiologists employ *causal inference*. Causal inference can be described as the process of drawing a cause-and-effect conclusion based on the results of epidemiologic research. An example of causal inference approach is the set of guidelines (or viewpoints) that was proposed by Bradford-Hill, a British epidemiologist and statistician. The types of factors that are typically considered when applying the Bradford-Hill viewpoints include presence or absence of a temporal relation between the independent and the dependent variable (exposure must precede the disease), strength of association (as measured by the magnitude of the relative risk or regression coefficient); dose-response (incidence of disease is expected to increase with increasing level of exposure) and replication (consistent results observed in different studies).

It is important to emphasize; however, that a discussion about causation can only begin once the association is well formulated. In other words, before getting into causal inference it is critical to understand the specific attributes of an association in terms of the exposure of interest, the health- related measure of concern and the population under investigation.

Evaluation of multiple associations

Traditional methodology of causal inference (e.g., Bradford-Hill criteria) and the accepted significance cutoffs for statistical inference (e.g., using a p-value of <0.05) work best in situations when the researchers are evaluating a pre-specified hypothesis about the association between one exposure and one outcome. In many instances, however, the available data allow evaluating many dependent and independent variables without a specific *a priori* hypothesis. This situation is often referred to as *multiple simultaneous hypothesis testing* or simply *multiplicity*. This feature of epidemiologic studies complicates interpretation of findings. When multiple associations are tested at the same time, it is virtually guaranteed that some of the associations will appear statistically significant simply by chance.

Consider, for example, a series of studies that evaluate differences in symptoms between two or more groups of people taking different medications. As the number of symptoms (e.g., headache, upset stomach, fatigue, etc.) evaluated in a particular study increases, it becomes more and more likely that the drugs in that study will appear different in terms of at least one symptom. This is not necessarily a problem if the association with a particular symptom is found and reported consistently across studies. However, the ability to make this determination depends on two factors: the comparability of analyses and the completeness of reporting. Suppose one study evaluating a particular drug collected data on 20 different symptoms, but reported a significant association only for headaches without mentioning results for the remaining 19 symptoms. Another study evaluating the same drug collected the data on the same

symptoms but only presented information on fatigue. An uncritical reviewer could have concluded that the drug in question is associated with both headaches and fatigue when in fact this may not be true because both of these results can be attributable to multiple hypothesis testing and incomplete reporting.

These types of problems are well known in the area of genetic epidemiology and in pharmacoepidemiology (a field of epidemiology that deals with risks and benefits of drugs). They also apply to environmental epidemiology generally and epidemiology of PCB exposures and neurodevelopmental measures in particular, as I will explain later in the report.

Principles of reviewing epidemiologic evidence

Any evaluation of a body of epidemiologic evidence begins by understanding the main research question, which includes three components: 1) What is the study population? 2) What is the exposure of interest? (3) What is the dependent variable of concern?

The next step in evaluating epidemiologic studies is a systematic search, retrieval and review of the relevant literature. It is critical to avoid "cherry-picking" so that all relevant studies are considered, regardless of the direction and statistical significance of the reported association.

It is also important to keep in mind that not all relevant studies can be considered equally valid. In conducting a review of the literature, all papers should be evaluated critically with respect to the study design, data collection procedures, analytical methods, and interpretation of results. As different studies have different strengths and limitations, it is essential to evaluate them as a group and base conclusions primarily on those that are stronger methodologically.

Although literature reviews may be categorized in various ways, the two main types are narrative and systematic. Traditional narrative reviews are not necessarily aimed at addressing a pre-specified hypothesis, and do not employ systematic and reproducible methods of literature search and retrieval. By contrast, a systematic review involves a more rigorous scientific process characterized by transparency and repeatability with the primary aim of minimizing error in addressing a particular research hypothesis.

When the data allow a numerical synthesis of results, a systematic review may include a meta-analysis, which in its most basic form represents a statistical integration of results from several independent studies investigating the same association. When the numerical (a.k.a. quantitative) results are not presented in consistent fashion, the available evidence can be evaluated qualitatively (i.e., by providing a description of findings in the text). Regardless of the methodology used to synthesize the evidence, a critical feature of a systematic review is proper identification and grouping of studies addressing the same specific research question.

METHODOLOGY USED IN THIS REPORT

Overall approach

As mentioned in the previous section, a distinguishing characteristic of a systematic assessment of epidemiologic evidence is proper grouping of studies addressing the same specific research question. Once studies are properly grouped with respect to their research question (or questions) they can be compared side-by-side to assess consistency.

The current guidelines for systematic assessments of the evidence recommend defining a research question using the PICOS acronym, where P denotes study population, I and C represent intervention and comparison groups, O is the outcome of interest and S specifies study design (Centre for Reviews and Dissemination 2009; Higgins and Green 2011). In a corresponding acronym more suitable for environmental research, intervention under study (I) is often replaced with (E) which denotes exposure of interest (LaKind et al. 2017).

The importance of properly applying the PI(E)COS framework is especially evident when reviewing the literature with multiple possible ways of defining and measuring exposures and health measures of interest across different population groups. Studies of polychlorinated biphenyls (PCBs) and neurodevelopmental test results in children represent a readily available example of a body of literature that can be captured in a myriad of possible PECOS statements.

With respect to population of interest (P), an important factor in assessing consistency within and across studies of neurodevelopment is age of participants. Infants and children of different ages may demonstrate different skills and domains of function even when evaluated by the same test. For example, in the widely used Bayley Scales of Infant Development III (BSID), cognitive domain administered in early infancy would compare levels of attention to new and familiar stimuli. By contrast, the BSID cognitive domain assessed in a child of preschool age would evaluate the ability to engage in pretend play (Bayley 2006).

Similar considerations apply to the various ways exposure to PCBs (E) is measured. The term 'PCB' describes 209 different congeners, which can be grouped in a variety of ways with respect to their hypothesized biological properties and/or chemical structure (Faroon et al. 2000; Longnecker et al. 2003; Negri et al. 2003). Moreover, these congeners or groups of congeners can be measured at different times (e.g., prenatally or at different ages), and in different types of biological specimens (e.g., in cord blood or breast milk).

A separate issue is the choice of comparisons (C) or categorization of exposure. For example, PCB measures can be divided into quartiles, expressed as ordinal variables or as binary 'high-low' categories, although the cutoffs for categorization may differ within and across studies. If PCB exposure is expressed as a continuous variable, there still may be considerable leeway in terms of imputing or not imputing values below the limit of detection, correcting or not correcting for lipid concentrations, adjusting or not adjusting for batch variability, and performing or not performing log-transformation of the data.

Perhaps the most important threat to inter-study and intra-study consistency is a lack of agreed-upon approach towards selecting the outcomes of interest (O). The term "neurodevelopment"

encompasses various domains of brain function within the normal range as well as clinical diagnoses (Institute of Medicine 2015). With respect to PCB literature specifically, most studies define "neurodevelopment" based on results of various tests administered at different ages. Assessment of consistency of studies that rely on neurodevelopmental tests is a particular challenge due to the large number of available test batteries, each offering different combinations of subtests (Goodman et al. 2010; Youngstrom et al. 2010) Further, if tests are used and reported selectively, it can be very difficult to determine whether two different studies or two different analyses within the same study produced similar or conflicting results (Garabrant 2000).

From the study design (S) perspective, an evaluation of a causal hypothesis depends on the ability to establish the proper sequence of exposure and outcome (Potischman and Weed 1999; Rothman and Greenland 2005; Weed and Gorelic 1996). There appears to be a consensus that when it comes to environmental exposures and neurodevelopment this can be achieved by conducting longitudinal birth cohort studies, especially if the hypothesized effect is attributable to *in utero* and early life exposures (Amler et al. 2006; Wigle et al. 2008).

A systematic evaluation of the evidence needs to take into account not only the apparent consistency or inconsistency of reported results, but also the possibility that not all available results were reported. The incomplete reporting of results may be attributed to publication bias, which is defined as the "tendency on the parts of investigators or editors to fail to publish study results on the basis of the direction or strength of the study findings" (Dickersin and Min 1993). Another closely related concept is selective within-study reporting defined as "selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication" (Dwan et al. 2008). The problems of selective publication and selective reporting may be especially acute when the researchers have the ability to test multiple exposure-outcome associations using a wide range of analytic approaches (Ioannidis 2012).

Based on all of the above considerations, this report is focused specifically on cohort studies that recruited participants either prenatally or soon after birth and linked various measures of PCB exposures to neurodevelopmental measures at different ages. The goals are to employ the PECOS framework to systematically assess consistency within and across results and to estimate the number and proportion of reported associations relative to all associations that could have been reported.

Identification and selection of studies

In preparation of this report, I conducted an electronic literature search using the US National Library of Medicine PubMed database and the international EMBASE database. The specific search terms of interest were "PCB cohort children" and "polychlorinated biphenyl cohort children".

The first PubMed search yielded 254 citations and the second search yielded 358 citations. After removal of 229 duplicates, a total of 383 unique PubMed citations were reviewed. The two corresponding EMBASE searches using the same combinations of keywords yielded 356 and 353 citations, respectively. Of those, 160 citations were unique (i.e., not found in PubMed). Secondary references of retrieved articles and review publications were also examined to identify studies not captured by the electronic search.

Studies were included in the report if they:

1. Were based on the data from a cohort of children who were recruited prenatally or at birth
2. Collected information on prenatal or postnatal measures of PCB exposure (including intake of PCBs with diet) in the general population and used these measures as the independent variables
3. Used dependent variables that were based on results of tests (e.g., Bayley Scales of Infant Development), components of tests (e.g., Block Design component of the Wechsler Intelligence Scale for Children), reporting or observation-based scales (e.g., Pre-School Activity Inventory), or specific diagnoses (e.g., attention deficit hyperactivity disorder)
4. Reported associations between one or more exposures of interest or one or more neurodevelopmental measures of concern in either qualitative or quantitative fashion[1]

Studies that evaluated measures not directly reflecting neurodevelopment (e.g. birth weight or thyroid hormone concentrations), cohorts of children identified and recruited later in life (e.g., in elementary school), and investigations of populations that suffered from PCB/PCDF poisoning due to accidents (e.g., children comprising the Yusho cohort) were excluded.

Literature review and data collection

A total of 110 publications were identified via the electronic and manual literature search and met the inclusion criteria. Data extracted from each relevant study were categorized according to the following characteristics:

- Cohort (e.g., name and geographic location)
- Publication (First author, year and full citation)
- Unique exposure categories including, whenever available, congener number(s), biological matrices, and timing (e.g., prenatal, perinatal or postnatal) of sample collection
- Source (page and/or table number) of information on each exposure used as the independent variable in at least one analysis
- Unique dependent variables including names of tests or scales and test/scale components
- Source (page and/or table number) of information on each measure used as the dependent variable in at least one analysis
- Age at which neurodevelopmental/neurobehavioral tests were administered

To estimate the number of all possible exposure-outcome associations, the total numbers of unique independent and dependent variables were multiplied with the product interpreted as the number of possible associations that could have been reproduced, at least in theory, across all studies. Each possible exposure-outcome association was then categorized as "reported" or "not reported/not evaluated." For each reported association, I identified the number of independent cohort studies that mentioned it in at least one of the published articles. This characterization of

[1] Quantitative result is defined as showing a numerical measures of association and/or a corresponding measure of statistical significance. Qualitative result is defined as mentioning the association in the text without providing a numerical value.

the literature allowed identification of reasonably homogeneous[2] groups of studies addressing the same associations within the same age group. The source of information on study results in these analyses was also documented by recording the page and/or table or figure number.

Previous research demonstrated that very few results in the PCB literature are reported quantitatively, which makes it impossible to conduct a meta-analyses (Goodman et al. 2010). For this reason, in this report the associations in each group were categorized in a qualitative fashion (i.e., in words rather than numbers). The result was labeled as "significant," if the measure of association was in a hypothesized direction and accompanied by a conventional two-sided type I error of <0.05. The result was considered "not significant/opposite" if the two-sided type I error was ≥ 0.05, or if the results were opposite of the hypothesized direction. The result was categorized as "mixed" if a study reported variable results across different statistical approaches, different subsets of participants, or for the same participants at different points in time within the same age group.

In reviewing this body of literature, and before drawing conclusions, I asked the following primary questions:

1. Are the same or similar results repeatedly observed and independently reported by different studies conducted in different populations?
2. Do the same or similar PCB exposures produce effects within the same group of children as these children grow older?
3. Is there evidence that in populations with higher PCB exposure levels, the association with neurodevelopmental test results is stronger or more commonly observed compared to populations with lower exposures?
4. Do the data show that PCB exposed children in the general population experience greater incidence of neurodevelopment-related diagnoses?

The first question addresses consistency of reporting and replication of results across studies. This issue is critical because, as explained previously, it is premature to begin discussing causation unless one or more specific well formulated associations are established.

The second question evaluates within study consistency. A particular association may be observed at a given age but no longer found when the same children are re-evaluated a bit later using the same or similar neurodevelopmental measure. If found repeatedly in different studies, such a discrepancy can be interpreted as evidence of a transient effect. If not replicated, this is usually a sign of a chance finding.

The third question also relates to the coherence of findings across studies with different levels of PCB exposure. If PCBs at background levels act as neurotoxic agents, populations exposed to higher levels (especially if measured using the same methods) would tend to experience greater extent of neurodevelopmental problems. This is not necessarily the same as 'dose-response' because the concept of dose-response implies that a specific association is addressed consistently across studies. Nevertheless, even if the studies are dissimilar, one would expect that research conducted in populations with higher exposure levels would tend to observe stronger results.

[2] The term 'homogeneous' describes studies that are similar in terms of methodology or results or both. The opposite term is 'heterogeneous'

The fourth question addresses the issue of clinical significance of findings. In the presence of multiple simultaneous hypothesis testing, some associations between PCB measures and test results are expected to be statistically significant. As I explained in the section "Statistical and clinical significance of associations", if the association with a particular neurodevelopmental measure (e.g., inattention, hyperactivity or impulsivity scales) is real, one would also expect a greater likelihood that children with higher levels of exposure are more likely to receive a clinical diagnosis of a related condition (e.g., attention deficit hyperactivity disorder).

If the answer to these four questions is "yes", the evidence can be viewed as supporting the causal relation between background PCB exposure and neurodevelopmental problems. If, however, the answer is 'no', the evidence has to be interpreted as indicating a likely artefact, which may be attributable to multiple hypothesis testing, flawed data, and/or incomplete reporting.

ARE THE SAME OR SIMILAR RESULTS REPORTED BY DIFFERENT STUDIES?

With respect to age of neurodevelopmental assessment the follow up can be divided into five intervals: newborns (under 1 month), infants (1-11 months); toddlers (12-35 months), preschoolers (3-5 years) and school age children (at least 6 years old). These groups are defined based on the generally accepted cutoffs (American Academy of Pediatrics 2019; Centers for Disease Control and Prevention 2019). The assessment of inter-study consistency is presented according to these age groups.

Newborns (0-4 weeks of age)

Nine cohorts examined the associations between PCB exposures and neurodevelopmental test results within the first month of life. Five of these cohorts were US-based and included populations from North Carolina (Rogan et al. 1986b), Michigan (Fein et al. 1984; Jacobson et al. 1984a), Oswego, NY (Lonky et al. 1996; Stewart et al. 2000), New York City (Engel et al. 2007), and New Bedford, Massachusetts (Sagiv et al. 2008) All five US cohorts administered Brazelton's Neonatal Behavioral Assessment Scale (NBAS), which includes 27 items each scored on a nine-point scale (Brazelton 1978). The various items are then combined to create seven clusters; six of those clusters – response decrement (a.k.a. habituation), orientation, motor performance, range of state, regulation of state, and autonomic maturity – are considered behavioral; and one cluster – reflex – is aimed at evaluating neurologic function (Lester et al. 1982).

When assessing the association between fish consumption and NBAS results, Jacobson and colleagues, reported findings for three of the seven clusters, although according to the Methods section all seven clusters were administered (Jacobson et al. 1984a). The results were internally inconsistent. For the reflex cluster, the result was statistically significant in the analyses of binary variables, but not in the regression model. For autonomic maturity, the pattern of results was reverse – a statistically significant association was observed in the regression model but not in a two-by-two table. The third reported cluster – range of states – was only examined in one of the two analyses (using binary variables); however, the reported p-value of 0.04 was calculated based on a chi square test, which is not suitable for sparse observations. When the same data are examined using a Fisher's exact test specifically developed for two-by-two tables with small numbers, the p-value is 0.09, and thus a more appropriate analytic approach should produce a non-significant result. The corresponding linear regression analyses for range of state were not reported at all. Instead the authors only present the results for one component of this cluster (lability of state) and omit the data for the other three components (peak of excitement, rapidity of buildup, and irritability).

The associations between fish consumption and NBAS were also examined in the Oswego cohort (Lonky et al. 1996). Although the resulting measures of association from the two cohorts cannot be compared quantitatively due to differences in statistical analyses, a qualitative assessment of inter-study consistency is possible. In the Oswego cohort, after controlling for confounders, significant associations with fish consumption were observed for response decrement (a.k.a. habituation), autonomic maturity and reflex cluster (Lonky et al. 1996). Recall that the corresponding adjusted association in the Michigan cohort (Jacobson et al. 1984a) was only reported for autonomic maturity, but not for the other two clusters. Moreover, the

association between fish consumption and lability of states that was highlighted in the Michigan study was not mentioned in the Oswego cohort.

None of the NBAS clusters in the Michigan cohort were associated with cord blood PCBs, but numeric results are not provided in the article (Jacobson et al. 1984a). In the Oswego cohort, the investigators examined the association between NBAS and cord blood PCBs using four metrics: total PCBs, lightly chlorinated (C11-C13) PCBs, moderately chlorinated (C14-C16) PCBs, and highly chlorinated (C17-C19) PCBs (Stewart et al. 2000). Unlike the previous study (Lonky et al. 1996) which defined dependent variable as the difference between the scores of the NBAS test administered on the 1st and 2nd days of life, the quantitative results in the Stewart et al (2000) publication were reported only for the second assessment. The authors do report that none of the measures were associated with NBAS administered on the first day of life. Two of the seven clusters (range of states and autonomic maturity) recorded on the second day of life were associated with PCB exposure, but only when the analyses were limited to C17-C19 compounds. By contrast, the results for total PCBs are not mentioned, and for other compounds the authors only state that lightly or moderately chlorinated PCBs were "not related to habituation, autonomic or abnormal reflex clusters."

The third US study (North Carolina cohort) administered NBAS between the first and third week of life (Rogan et al. 1986b). The prenatal PCB exposure in that study was assessed based on estimated concentrations in breast milk fat at birth (using, whenever available, actual measures in maternal blood, cord blood, placenta and breastmilk). The authors reported that higher PCB exposures were associated with NBAS motor (a.k.a. tonicity) and reflex clusters. It is important to point out that these conclusions are not fully supported by the statistical analyses. Although proportions of subjects with lower motor scores were higher in individuals with higher PCB exposure, the differences did not approach statistical significance with calculated p-values for motor cluster and its components of 0.4 or higher. The corresponding p-values for reflexes were all 0.16 or higher.

The Mount Sinai Children's Environmental Health Cohort study enrolled women who presented for prenatal care at one of the affiliated outpatient facilities in New York City (Engel et al. 2007). PCBs in that study were measured in maternal blood and expressed as a sum of congeners 118, 138, 153 and 180. None of the associations with NBAS clusters were statistically significant in the hypothesized direction. The authors pointed out that for one of the clusters, range of state, the association was "…in an unexpected direction. Increasing PCB level was positively associated with an improved range of state, in a dose dependent manner."

The most recent of the US based studies evaluating the association between PCB exposure and NBAS was conducted in New Bedford, Massachusetts (Sagiv et al. 2008). The focus of the analysis was not on the typical NBAS clusters but rather on subscales or newly created endpoints such as "consolability" or "never in state to do orientation items". With respect to consistency with other studies the only comparable results are provided in relation to three NBAS components – orientation, habituation, and regulation of state. No numerical results are included; the authors only state: "There were no consistent associations between organochlorines and any of the three cluster measures (orientation, habituation, and regulation of state; data not shown)"

One study based outside of the United States also used NBAS. In that study, carried out in the Tohoku district of Japan, cord blood samples were analyzed for all 209 PCB congeners, and the sum of all measured congeners was used as the exposure variable (Suzuki et al. 2010). The crude (unadjusted) analyses demonstrated statistically significant associations for three NBAS clusters: orientation, regulation of state, and motor; however for the first two of these clusters the associations were in opposite to hypothesized direction. When the data for motor cluster were examined in a series of multivariable analyses the previously observed association with PCBs was no longer statistically significant, and even changed direction in the fully adjusted model.

The three European cohorts evaluating neurodevelopment among newborns were conducted in Duisburg, Germany (Wilhelm et al. 2008b), Rotterdam and Groningen in the Netherlands (Huisman et al. 1995a), and the Faroe Islands (Steuerwald et al. 2000). All three studies used the neurologic optimality score (NOS) that consists of 60 components (Touwen et al. 1980). All three European studies conducted the NOS assessment between 10 and 28 days of life and all three measured PCBs in breast milk and in maternal blood. In addition, two of the three European studies (Huisman et al. 1995a; Steuerwald et al. 2000) also performed laboratory analyses of cord blood samples, but only one (Huisman et al. 1995a) reported the results for these measures of PCB exposure.

The Rotterdam/Groningen cohort reported results for multiple exposure metrics (Huisman et al. 1995a). These included levels of all PCBs, various PCB subsets (e.g., planar versus nonplanar) and individual congeners in breast milk as well as PCB-138, 118, 153 and 180 (alone and in combination) measured in maternal and cord blood samples. The overall NOS was significantly associated with PCB-70, 99, 138, 153, 156, 169, 170, 177, 183 and 187 in breast milk, but not with PCB-28, 52, 66, 101, 105, 118, 126, 128, 137, 141, 151, 180, 194, 195 or 202. Moreover, the significant associations observed for breast milk PCB-118, 138 and 153 were not confirmed in the analysis of cord or maternal blood levels.

The associations of NOS and breast milk PCB-138 and PCB-153 observed in the Dutch study were not confirmed in a similarly designed birth cohort study from Duisburg, Germany (Wilhelm et al. 2008b). In addition, none of the associations with maternal blood PCBs (individually or in combination) in that study were statistically significantly associated with lower scores on any of the tests.

Unlike their Dutch and German colleagues, the investigators of the Faroe Islands cohort study (Steuerwald et al. 2000) did not include associations with individual PCB congeners. The only exposure metric included in that study was the total PCB concentration, which was estimated as the sum of PCB 138, 153 and 180 multiplied by 2. Neither maternal blood nor breast milk PCBs levels were associated with NOS.

In summary, studies that administered various tests in the newborn period found no consistent associations. Based on all possible measures of exposure and all possible test and subtest results these studies could have reported as many as 1,450 different associations; however, only 19 of those associations were reported by at least two cohorts; 12 of those association were consistently non-significant, and for the remaining seven the results were conflicting or mixed without a coherent pattern.

Infants (1-11 months of age)

The data for infants were examined in nine cohorts (Berghuis et al. 2013; Berghuis et al. 2014; Boucher et al. 2014; Daniels et al. 2003; Darvill et al. 2000; Gladen et al. 1988; Jacobson et al. 1985; Jacobson et al. 1986; Koopman-Esseboom et al. 1996; Nakajima et al. 2006; Nakajima et al. 2017; Walkowiak et al. 2001; Winneke et al. 1998).

Several cohort studies used the same test, Bayley Scales of Infant Development (BSID), to assess the neurodevelopment of their participants, and thus could provide comparable data. The BSID assessment was reported separately for two components – the Mental Development Index (MDI), which measures cognitive, language, and social development, and the Psychomotor Development Index (PDI) which measures fine and gross motor skills.

Three of these studies were conducted in the United States. The Michigan and the North Carolina cohort studies were discussed previously in the context of neonatal assessment. The third U.S. study (Daniels et al. 2003) represents a multicenter effort—called the Collaborative Perinatal Project—that recruited participants from eleven US cities (Baltimore, MD; Boston, MA; Buffalo, NY; Memphis, TN; Minneapolis, MN; New Orleans, LA; New York, NY; Philadelphia, PA; Portland, OR; Providence, RI; and Richmond, VA).

Among the three European analyses, two were carried out using the data from the same cohort in Dusseldorf, Germany (Walkowiak et al. 2001; Winneke et al. 1998), and one was conducted using the Rotterdam subset of the previously discussed cohort of Dutch children (Koopman-Esseboom et al. 1996). Two studies (Nakajima et al. 2006; Nakajima et al. 2017) were performed with a cohort of children from Sapporo, Japan (the Hokkaido Study on Environment and Children's Health). In addition, one recent publication (Boucher et al. 2014) assessed the association between PCB exposure and BSID scores among Inuit children from three villages in Nunavik (part of Northern Quebec), Canada.

In the Michigan cohort (Jacobson et al. 1986) exposure was characterized as a sum of unspecified PCB congeners in cord blood, PCB intake via nursing, and reported fish consumption. Numeric results and the directions of the observed associations at 5 months of age are not reported. The authors only stated: "None of the measures of prenatal PCB exposure were related to the Mental Development Index (MDI) or the Psychomotor Development Index (PDI) on the Bayley Scales."

In the North Carolina cohort (Gladen et al. 1988), BSID was administered at 6 months of age. Independent variables were expressed in two ways: (1) as a sum of unspecified PCBs in breast milk fat at birth calculated based on an average of various samples (maternal blood, cord blood, placenta and breastmilk); and (2) as an estimated cumulative exposure to PCB in breast milk from birth to the age of testing. The first exposure metric was associated with statistically significantly lower PDI, but not MDI. Neither BSID scale was associated with the second exposure metric.

The Collaborative Perinatal Project followed the neurologic development of approximately 44,000 US children born in 1959-1966 (Daniels et al. 2003). All eligible participants had BSID

testing at the age of 8 months and all had prenatal maternal blood samples available for analysis. Maternal blood PCBs levels were measured in a randomly selected subsample of 1207 participants with a range of BSID scores. Exposure was expressed as a sum of 11 PCB congeners (28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) as well as each congener individually. None of the exposure metrics were significantly associated with either MDI or PDI. The results by site varied widely, with regression coefficients ranging from statistically significant positive to statistically significant negative.

Two different publications reported results based on the Dusseldorf cohort (Walkowiak et al. 2001; Winneke et al. 1998). BSID was administered at the age of 7 months and PCB exposure was expressed as sum of three congeners (138, 153 and 180) in cord blood and maternal milk. All statistical results were accompanied by one-sided tests.[3] In the earlier study (Winneke et al. 1998) the authors reported "significant negative associations" between PCB in milk and MDI, but the one sided p-value was 0.048, indicating that a conventional two-sided statistical analysis would have produced a p-value of approximately 0.1. The result for PDI in relation to breast milk PCB, and both MDI and PDI results in relation to cord levels were not statistically significant or in the opposite direction. The more recent study (Walkowiak et al. 2001) assessed the same association, but the number of participants included in the second analysis was much smaller (110 instead of 171). None of the associations with BSID administered at 7 months of age in that second study were statistically significant.

The Rotterdam cohort participants underwent BSID testing twice during infancy, at 3 and 7 months of age (Koopman-Esseboom et al. 1996). Exposure was characterized as sum of four PCB congeners (118, 138, 153 and 180) measured in three types of samples – maternal blood, cord blood and breast milk. Among 12 different results (3 types of samples × 2 ages × 2 BSID subsets) only one – PDI at 3 months of age in relation to maternal blood PCB – demonstrated a statistically significant association. Importantly, the association observed at 3 months of age was no longer present at 7 months, although the numeric result for the second analysis is not reported.

Another study that performed BSID testing around 6 months of age was conducted on the island of Hokkaido, Japan (Nakajima et al. 2006; Nakajima et al. 2017). PCB exposure was assessed by measuring 14 different congeners. Individual congeners were categorized as non-ortho (77, 81, 126, and 169), mono-ortho (105, 114, 118, 123, 156, 157, 167, and 189) and di-ortho (170 and 180) PCBs. Associations with MDI and PDI scores were examined for each congener separately (except PCB-81, which was not detected) and for three different combinations (non-ortho, mono-ortho and total coplanar). These combinations of PCBs were further expressed in two ways: as pg/g lipid and as TEQs. Of the 38 reported associations (2 BSID scores × [13 individual PCB congeners + 6 combinations) in the first analysis (Nakajima et al. 2006), none was statistically significant. In a more recent study (Nakajima et al. 2017), the results were reported separately for boys and girls. Among all reported associations, several were statistically significant in boys but not girls, and one was significant in girls, but not boys.

Unlike other studies, exposure assessment in the Nunavik cohort (Boucher et al. 2014) focused on only one congener (PCB-153) measured in cord blood samples. The BSID testing was

[3] Note that conventional cutoff for statistical significance is based on a two-sided test. A one-sided p-value is half the corresponding two-sided p-value.

performed at 11 months of age. Neither MDI nor PDI was associated with PCB-153 cord blood levels in that study.

In addition to BSID, the children in the Nunavik study also underwent the A-not-B test and the Fagan Test of Infant Intelligence (FTII). Whereas the A-not-B test was never used in any other study, the FTII results were reported previously, and thus offer another opportunity to assess inter-cohort consistency.

During FTII administration, the infant is shown two identical photos and is then presented with the familiar photo paired with a new one. Based on the child's fixation on the images, two measures are computed; the first, termed "novelty score," is the percentage of time devoted to looking at the novel stimulus and the second, "fixation duration," is defined as the average time spent looking at all of the stimuli (Boucher et al. 2014). The children enrolled in the Nunavik underwent FTII testing twice – at 6.5 and 11 months of age. Based on Figure 1, the results for FTII novelty preference were not statistically significant at either age. The corresponding results for fixation time are not reported. When both ages were taken into consideration, there was a statistically significant inverse association with cord blood PCB-153 for novelty, but a null result for fixation time.

Three earlier cohort studies also evaluated their participants using the FTII (Darvill et al. 2000; Jacobson et al. 1985; Winneke et al. 1998). Unlike the Nunavik cohort, none of these earlier studies focused specifically on PCB-153, and used different exposure metrics and different statistical approaches.

In the Michigan cohort (Jacobson et al. 1985) FTII was administered at 7 months of age and the reported results are limited to the novelty score. Exposure was expressed as self-reported fish consumption and the sum of unspecified cord blood and breast milk PCBs. There was a statistically significant inverse association between exposure and FTII novelty score for the first two of the three exposure measures.

Another US-based study that used data from the Oswego, NY cohort (Darvill et al. 2000) administered FTII at the age of 6 months. Although the authors refer to the FTII result as "fixation score", based on the testing description it appears that they used novelty score as the dependent variable of interest. Exposure was characterized as a sum of all measured PCB congeners or as total highly (septa-, octa-, and nona-) chlorinated PCBs in cord blood as well as all measured PCBs in breast milk. FTII was significantly associated with sum of all measured, but not highly chlorinated, PCBs in cord blood. No significant associations were observed with regards to fish consumption or breast milk PCBs. Although the authors state that their study was specifically designed to replicate findings from the Michigan cohort (Jacobson et al. 1985), the results of the two studies are not directly comparable due to differences in statistical analysis and exposure categorization (with the exception of fish consumption). Whereas Michigan investigators used multiple linear regression and treated PCB level as a continuous variable, Darvill and colleagues performed an F-test for trend that used a four-level exposure categorization. The PCB measures in the two studies were also different. The Oswego investigators reported analyzing 68 PCB congeners and examined them as a sum, while congener composition in the Michigan study was not reported. Fish consumption data were collected in both the Michigan and the Oswego cohorts (see previous section); however, only Michigan

investigators reported a statistically significant association between this exposure metric and FTII.

One additional report on the association between PCB exposure and FTII novelty score is available from Dusseldorf cohort (Winneke et al. 1998). As mentioned previously, the PCB exposure in that study was expressed as sum of three congeners (138, 153 and 180) in cord blood and breast milk. Neither exposure metric in that study was associated with a statistically significantly lower FTII result.

In summary, studies that administered various tests between 1 and 11 months of age collectively included the data on 2,542 possible associations. Only 9 of these associations were reported by 2 or more cohorts; in 8 instances all results were not statistically significant, and in one instance the results were conflicting.

Toddlers (12-35 months of age)

Seventeen cohorts examined the association between various measures of PCB exposure and neurodevelopmental measures in toddlers. These cohorts were described in 21 publications (Brucker-Davis et al. 2015; Darvill et al. 2000; Forns et al. 2012a; Forns et al. 2016; Gascon et al. 2014; Gladen et al. 1988; Huisman et al. 1995b; Kim et al. 2018; Koopman-Esseboom et al. 1996; Lynch et al. 2012; Nakajima et al. 2017; Pan et al. 2009; Park et al. 2009; Park et al. 2010; Ribas-Fito et al. 2003; Rogan and Gladen 1991; Ruel et al. 2019; Tatsuta et al. 2012; Walkowiak et al. 2001; Wilhelm et al. 2008a; Wilhelm et al. 2008b).

As in the previous age group, several studies used BSID as a measure of neurodevelopment. In the North Carolina cohort, in addition to testing children at the age of 6 months, the investigators also administered BSID at 12 months (Gladen et al. 1988) and then again at 18 and 24 months of age (Rogan and Gladen 1991). Transplacental exposure was estimated based on available measures in maternal blood, cord blood, placenta and breastmilk and expressed as PCB concentrations in breast milk fat. Cumulative exposure was calculated based on PCB concentrations in breast milk and duration of breastfeeding. The first exposure metric was associated with statistically significantly lower PDI at 12 months in the earlier study (Gladen et al. 1988). By contrast the same association was less evident at 18 and 24 months of age (Rogan and Gladen 1991). The authors asserted that the result at 24 months of age was significant; however, a closer inspection of the data indicates that the confidence intervals around the differences between the lowest exposure category and all subsequent categories (including the highest) overlapped the null value. Moreover, the difference for the highest exposure category was less pronounced than the corresponding difference for the previous category. None of the analyses for MDI were statistically significant, nor were the results for post-natal exposure.

The results for BSID at 18 months of age are also reported for the Rotterdam cohort (Koopman-Esseboom et al. 1996). As discussed previously, exposure in that study was measured as a sum of PCB-118, 138, 153 and 180 in maternal blood, cord blood and breast milk. Although the quantitative results are not reported, the authors state that neither MDI nor PDI was related to any of the exposure metrics.

In a more recent study based on two birth cohorts, also located in the northern part of the Netherlands, but assembled much later, BSID was administered at 18 and 30 months of age (Ruel et al. 2019). PCBs exposure in that study was based on maternal blood levels and included six hydroxylated PCBs (4-OH-PCB-107, 4-OH-PCB-146, 3-OH-PCB-138, 3-OH-PCB-153, 4-OH-PCB-172, and 4-OH-PCB-187), ten congeners (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and four combined measures. The four combined measures included sums of all 6 OH-PCBs and all 10 PCB congeners; a sum of dioxin like PCBs (105, 118 and 156); and a sum of non-dioxin like PCBs (138, 146, 153, 170, 180, 183, 187). Each of the twenty exposure metrics was examined in relation to MDI and PDI at 18 and 30 months of age and presented as crude and (in some instances) adjusted measures of association. In addition, the results were sometimes presented separately for each of the two cohorts. Nearly all of these results showed no association. Only one adjusted result – for MDI and PCB-153 was statistically significant, and only at the age of 18 months and only in one of the two cohorts; well within a range that would be expected by chance.

Two cohort studies from Germany also used BSID as the dependent variable of interest. In addition to evaluating participants at the age of 7 months (discussed in the previous section), the Dusseldorf cohort study (Walkowiak et al. 2001) administered BSID at 18 and 30 months of age. The analyses were conducted for two exposure metrics (sum of PCB-138, 153 and 180 in breast milk and cord blood) for each age separately and also across all age groups combined. One analysis – MDI and PDI in relation to breast milk PCB for all age groups (7, 18 and 30 months) – demonstrated a statistically significant association. The corresponding results for both MDI and PDI at 18 and 30 months of age considered separately were not statistically significant. When discussing results for cord blood the authors state "All associations with cord blood PCB and the Bayley Scales of Infant Development mental score were small and even slightly positive. Association between the Bayley Scales of Infant Development motor score and PCB was negative and very small."

The associations between breast milk PCBs and BSID in the Dusseldorf cohort were also reported in a more recent publication, which also included data from the Duisburg cohort (Wilhelm et al. 2008a). The Duisburg cohort was discussed earlier in the report, because the participants in that study were initially evaluated at 2 weeks of age using NOS (Wilhelm et al. 2008b). The same cohort underwent NOS testing at 18 months of age and BSID at ages 12 and 24 months. Exposure in the Duisburg cohort was assessed using a multitude of methods using both individual congeners and various combinations of PCBs in maternal blood and breast milk (a total of 44 measures). None of the analyses demonstrated a significant association between exposure and neurodevelopmental testing results.

The INMA (INfancia y Medio Ambiente [Environment and Childhood]) cohort recruited pregnant women in several regions of Spain and followed their children from birth. Results for a subset of the INMA cohort participants (limited to one of the study sites) were reported in 2003 and expressed PCB exposure as a sum of congeners 28, 52, 101, 118, 138, 153, and 180 in cord blood (Ribas-Fito et al. 2003). The results for BSID administered at the age of 13 months were significant only in the unadjusted analyses; however, after the associations were controlled for confounding factors, none of the associations were statistically significant. The first evaluation of children in the full INMA cohort was reported when they were "around 14 months" of age (Forns et al. 2012a). The associations with BSID in the full cohort were examined for maternal

blood levels of PCB-138, 153 and 180 and the sum of three congeners. The data for the sum of PCBs were also analyzed in a multipollutant model that controlled for co-exposures to hexachlorobenzene (HCB), and dichlorodiphenyl dichloroethylene (pp′DDE). The association with PDI was statistically significant for the sum of three PCBs in the single exposure model, but not in the multipollutant model. The associations with MDI were not statistically significant. More recently, the INMA cohort data were re-examined using a pharmacokinetic model, which takes into account the absorption, distribution, metabolism and excretion of PCBs to estimate postnatal exposure at different ages (Gascon et al. 2013). Only PCB-153 was considered in the model and none of the results were statistically significant. Unlike the earlier INMA cohort-based study (Forns et al. 2012a), the results for PDI and maternal blood PCB-153 in the more recent publication (Gascon et al. 2013) were statistically significant; however, the second analysis was based on a smaller sample (1175 vs. 1391).

Data from a clinical trial of iodine supplementation conducted in France were used to examine the association between breast milk PCBs and Bayley Scales of Infant and Toddler Development (a more recent version of BSID) at 2 years of age (Brucker-Davis et al. 2015). Neither cognitive nor motor scales (presumably equivalents of MDI and PDI, respectively) were associated with PCBs congeners, which included 153, 118, 138, 153, 180 and a sum of 77 and 126. PCB 118 was associated with two subscales – Language and Receptive Language, but these were the only significant results among 40 different associations examined in that study. The magnitude and direction of other associations were not reported.

The association of prenatal and post-natal PCB levels and BSID at 24 months of age was examined among participants in the New York State Angler Cohort Study (NYSACS), which enrolled over 2,500 women (Lynch et al. 2012). Of those, 102 women were recruited during pregnancy, but the data for the BSID analyses were available on only 44 mother-child pairs. Maternal serum samples collected during the first prenatal visit were analyzed for 74 different PCB congeners, and breast milk samples were analyzed for 209 congeners. The associations with BSID were examined for total PCBs in both types of samples. In addition, the data were analyzed for PCB-153, PCB-118, and for PCB-156/171 combination in maternal blood, as well as the PCB153/168 combination in breast milk. Of the 12 associations reported in the article, only one (PDI in relation to PCB153/168 in breast milk) demonstrated a statistically significant association.

The previously discussed study in Hokkaido, Japan (Nakajima et al. 2017) re-administered the BSID test at 18 months of age. Unlike the 6-month examination, none of the results for PDI were statistically significant. For MDI, six associations among girls were statistically significant, but all six were in opposite of the hypothesized direction (i.e., higher PCBs exposure were associated with better test performance).

Two publications (Park et al. 2009; Park et al. 2010) were based on the cohort of children in Slovakia. The first study (Park et al. 2009) measured exposure based on levels of hydroxylated PCBs in maternal and cord blood. The association with BSID was significant for one hydroxylated congener (4-OH-PCB-107), but not for OH-PCB-153, 146, 138, 187 and 172 and not for the combination of all six OH-PCBs. The second study (Park et al. 2010) measured non-hydroxylated PCB congeners in cord and maternal blood. The analyses demonstrated statistically significant associations for both PDI and MDI with PCB-118, PCB-156 and the

combination of these two congeners. In addition, there was a statistically significant association between cord blood (but not maternal blood) PCB-138 and PDI. None of the associations for PCB-153, PCB-170 and PCB-180 and for combinations of most common or presumably anti-estrogenic congeners were statistically significant.

A birth cohort study in South Korea administered BSID in the second year of participants' life (Kim et al. 2018). PCB congeners 28, 118, 138, and 153 were measured in maternal blood and congeners 118, 138, 153 180 were measured in breast milk. None the associations with either MDI or PDI, for PCBs considered individually or as a sum was reported to be statistically significant in the hypothesized direction.

The same South Korean study also evaluated the association of maternal blood and breast milk PCBs with Child Behavior Checklist (CBCL). CBCL is based on parent reporting and includes an internalizing behaviors score (emotionally reactive, anxious/depressed, somatic complaints, and withdrawn), externalizing behaviors score (attention and aggressive), a separate sleep problems score and the total score (Kim et al. 2018). Of the 70 associations examined in that study, three were statistically significant; these include the results for maternal blood PCB-153 and externalizing and total scores and for the sum of four measured congeners in maternal blood and externalizing score. None of the remaining congeners in maternal blood and none of the PCBs in breast milk were associated with any of the CBCL scores.

Another study that administered CBCL in the toddler age group was based on the Tohoku cohort in Japan (Tatsuta et al. 2012). PCB exposure in that study was expressed as a sum of all measured congeners in cord blood. In the unadjusted analyses, sum of cord blood PCBs was significantly correlated with the internalizing, but not with the externalizing or the total scores. The association with internalizing score was no longer evident once the results were controlled for confounders. The authors also mention that the results for PCB-153 were similar to those observed for the sum of all measured congeners. No data on other individual congeners are presented.

Two European cohort studies in Duisburg, Germany (Wilhelm et al. 2008a) and the Netherlands (Huisman et al. 1995b) used the previously discussed NOS test to examine participants at 18 months of age. The Rotterdam/Groningen cohort of Dutch children reported a statistically significant inverse association between prenatal PCB exposure (measured as a sum of 118, 138, 153 and 180 congeners in cord or maternal blood samples), but only among children whose fathers were not smokers and not among children of fathers who were smokers (Huisman et al. 1995b). No significant associations were observed for breast milk PCBs in that study. None of the associations with individual PCBs or combinations of congeners in the Duisburg cohort were significantly associated with NOS (Wilhelm et al. 2008a).

In summary, as children get older the number of possible associations continues to increase. In the toddler age group there were a total of 2,976 possible associations. Only 48 of those (2%) were examined by two or more studies. Of those 35 were consistently not significant or in the opposite of the hypothesized direction; the remaining 13 were conflicting; none of the significant results were replicated.

Preschool age (3-5 years)

The Michigan, North Carolina, Oswego, CPP, Nunavik, Rotterdam/Groningen, INMA, Dusseldorf, Slovakia, Northern Netherlands, Tohoku and Hokkaido cohorts re-examined their participants between the third and the sixth birthday. (Despres et al. 2005; Forns et al. 2012c; Gladen and Rogan 1991; Gray et al. 2005; Ikeno et al. 2018; Jacobson et al. 1990; Jacobson et al. 1992; Jacobson and Jacobson 2002a, b, 2003; Jusko et al. 2014; Kostiakova et al. 2016; Lanting et al. 1998; Patandin et al. 1999; Plusquellec et al. 2010; Roze et al. 2009; Saint-Amour et al. 2006; Sisto et al. 2015; Stewart et al. 2003a; Stewart et al. 2003b; Tatsuta et al. 2014; Walkowiak et al. 2001; Winneke et al. 2005). In addition, several birth cohorts (two in the US and one each in Greece, Canada, and Norway) presented their findings for the first time in preschool age (Bernardo et al. 2019; Braun et al. 2014; Caspersen et al. 2016a; Caspersen et al. 2016b; Granillo et al. 2019; Kyriklaki et al. 2016; Zhang et al. 2017) There were multiple neurodevelopmental measures reported across cohorts; however, only a few of those tests were administered in more than one population to allow an assessment of inter-study consistency.

Six cohorts – Michigan (Jacobson et al. 1990; Jacobson and Jacobson 2002a, b), Oswego (Stewart et al. 2003b), North Carolina (Gladen and Rogan 1991), Nunavik (Despres et al. 2005), INMA (Forns et al. 2012c) and a recent study conducted in Crete, Greece (Kyriklaki et al. 2016) evaluated cognitive function of their participants using McCarthy Scales of Children's Abilities (MSCA), which may be presented as Global Cognitive Index (GCI) or divided into Verbal, Quantitative, Perceptual–Performance, Memory, and Motor scales (Gladen and Rogan 1991; Stewart et al. 2003b). Exposure was assessed by measuring PCBs in breast milk, and in cord, maternal, and child's blood samples.

When evaluating cord blood samples, the Michigan cohort reported statistically significant inverse associations between unspecified cord blood PCBs and Verbal and Memory subscales of MSCA, but not for GCI and not for the Quantitative, Perceptual–Performance, and Motor subscales, all assessed at 4 years age (Jacobson et al. 1990). In the Oswego, NY cohort study results for total cord blood PCBs were not reported (Stewart et al. 2003b). Instead, analyses presented in the paper were limited to C17-C19 congeners. Inverse associations were observed for GCI and Quantitative and Perceptual–Performance subscales, but not for Verbal and Memory subscales. Moreover, the statistically significant associations were present at 3 years of age, but in none of the corresponding analyses at the age of 4.5 years. The third study assessing the association between cord blood PCBs and MSCA results was based on the data from the INMA cohort (Forns et al. 2012c). The study reported lower MSCA scores for GCI and several subscales (Verbal, Quantitative, Perceptual–Performance and Memory) but only in relation to one specific congener – PCB-153. With one exception (PCB-138 and Perceptual–Performance) all other analyses, which focused on PCB-118, 138 and 180, and the sum of all congeners, produced null results.

Two US-based cohort studies (Michigan and North Carolina), relied on a composite measure of prenatal/transplacental PCB exposure, which was based on sum of PCBs detected in cord blood, maternal blood and breast milk. In the Michigan cohort, the authors reported a statistically significant inverse association with GCI and for Verbal, Quantitative and Memory subscales, but only among 4-year-old children who were breast-fed for less than 6 weeks, and not among those who were nursing for a longer period of time (Jacobson and Jacobson 2002b). When the same

data were further subdivided based on maternal verbal competence using the Peabody Vocabulary score of 89 as the cutoff and by gender the results were also inconsistent (Jacobson and Jacobson 2002a). For example, regression coefficients for Quantitative and Memory subscales were significant only in children born to mothers with Peabody Vocabulary scores of at least 89; whereas correlation with Perceptual Performance was only statistically significant in children whose mothers scored low (<89) on the Peabody Vocabulary test. The equivalent analyses conducted at ages 3, 4 and 5 years in the North Carolina cohort demonstrated "no association" although details are not provided (Gladen and Rogan 1991).

Other exposures examined in relation to MSCA included PCB blood levels detected in children at the time of test administration and measures of intake via breastmilk. The former was examined in the Michigan and the INMA cohorts, which both reported null results (Forns et al. 2012c; Jacobson et al. 1990). The latter was used in Michigan and North Carolina cohorts, but based on different measures of exposure. The Michigan investigators (Jacobson et al. 1990) reported a statistically significant inverse association between unspecified PCB concentrations in breast milk and one of the six MSCA measures (Memory subscale) at 4 years of age. In the North Carolina study (Gladen and Rogan 1991) breast milk PCBs were measured in terms of cumulative exposure; none of the associations with MSCA scores were statistically significant at 3 years of age. The quantitative results at 4 and 5 years of age are not presented, but the authors state "In these same children at 4 and 5 years of age, no relationship to PCBs was found" (Gladen and Rogan 1991).

Two European cohorts (Dusseldorf, Germany and Rotterdam/Groningen, Netherlands) and two Japanese studies used Kaufman Assessment Battery for Children (KAB-C) as the neurodevelopmental measure of interest. The KAB-C test assesses two types of functioning – sequential and simultaneous; the results of each type of testing may then be combined to calculate the overall cognitive score.

In the Dutch cohort, results of KAB-C testing at 3.5 years of age were statistically significantly associated with sum of PCBs in maternal and cord blood samples, but only among children who were formula fed since birth (Patandin et al. 1999). In the Dusseldorf cohort (Walkowiak et al. 2001) the associations between cord blood PCBs and KAB-C at the same age were described as "small and even slightly positive". The inverse association between KAB-C and PCBs measured in children's blood samples was observed, although technically not significant (two-sided p-value=0.05) in Dusseldorf (Walkowiak et al. 2001), but no association was observed in the Rotterdam/Groningen study (Patandin et al. 1999).

When the KAB-C data were examined in relation to breast milk PCBs, all of the analyses in the Rotterdam/Groningen cohort produced statistically non-significant results (Patandin et al. 1999). The Dusseldorf cohort (Walkowiak et al. 2001) indicated that the results were statistically significant for both PCB breast milk concentrations and cumulative intake measures, but this interpretation was based on one-sided tests, whereas two-sided p-values were >0.05.

The Japanese version of the KAB-C test at the age of 3.5 years was examined in relation to multiple measures of PCBs in maternal blood in the Hokkaido cohort (Ikeno et al. 2018). The KAB-C results were categorized in two ways: as an overall mental processing summary scale (a.k.a. overall cognitive score) and an achievement scale. All associations were presented both

overall and separately for boys and girls, each expressed as two measures: a correlation and a regression coefficient. Only one of these multiple associations (between the sum of non-ortho PCBs and the overall mental processing summary scale among boys) was statistically significant and inverse. Several associations, especially for achievement scale among girls, were statistically significant, but in the opposite direction, indicating better performance in those with higher PCB exposure.

Another study conducted in Japan also administered KAB-C at 3.5 years of age (Tatsuta et al. 2014). Participants in that study were enrolled in the previously discussed Tohoku cohort, but unlike previous publications (Suzuki et al. 2010; Tatsuta et al. 2012), exposure in that article was expressed in terms of PCB homologs: monochlorobiphenyl (1 CB), dichlorobiphenyl (2 CB), trichlorobiphenyl (3 CB), etc. Only the association with one of the ten homolog groups (9 CB) was statistically significant for two of the four KAB-C scales - sequential processing score and the overall cognitive (termed "mental processing") scale. Moreover, the association between 9 CB and mental processing was only evident in boys and not in girls (Tatsuta et al. 2014).

Besides MSCA and KAB-C, the studies in this age category examined multiple other neurodevelopmental measures. Only a few of those measures were addressed in more than one population.

The CPP cohort participants underwent Stanford-Binet IQ test at 4 years (Gray et al. 2005). The association between the sum of PCBs (congeners 28, 52, 74, 105, 118, 138, 153, 170, 180, 194 and 203) in maternal blood and test results was statistically significant, but in the opposite of the hypothesized direction (i.e., children with higher prenatal exposure to PCBs had significantly higher IQs relative to children with lower PCB exposure levels). Another study relying on the Stanford-Binet test was conducted in Norway (Caspersen et al. 2016a). PCB exposure in that study was based on PCB-153 intake ascertained by combining self-reported information on consumption of various foods with the data on concentrations of PCBs in Norwegian diet. Unlike the CPP cohort, Stanford-Binet measures in the Norwegian study included, in addition to Total IQ, verbal and non-verbal IQ components as well as Working Memory Index along with separate scores for verbal and non-verbal working memory. None of the associations between these Stanford-Binet scores and dietary PCB-153 were statistically significant.

The Health Outcomes and Measures of the Environment (HOME) study is a birth cohort of children residing in Cincinnati, Ohio (Braun et al. 2014). The study collected maternal blood and urine samples and performed a number of laboratory analyses for a range of chemicals. PCB exposures were estimated based on maternal blood levels of 25 congeners or congener combinations (28, 66, 74, 99, 101, 105, 118, 138/158, 146, 153, 156, 157, 167, 170, 172, 177, 178, 183, 187, 194, 195, 196/203, 199, 206, 209). Each of these exposure metrics was examined in relation to Social Responsiveness Scale (SRS), which relies on maternal report to ascertain problems consistent with autistic behaviors. Each association was examined using 10 alternative statistical models. Only one association, with PCB 138/158, was statistically significant in 2 of the 10 models. On the other hand, several associations (e.g., with PCB 178 in three multipollutant models) were significant in opposite direction. Another study that used SRS was conducted in ten Canadian cities among children enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study (Bernardo et al. 2019). Exposures of interest were defined as maternal blood concentrations of PCBs 118, 138, 153, 170, 180 and 187, evaluated

individually and as a sum of all congeners. As in the HOME study each association was examined via several alternative models with SRS score expressed as a continuous or binary variable, and for binary SRS using both traditional frequentist and Bayesian approach. In only one of these analyses – for the association between PCB 153 and SRS score >60 in the Bayesian model – the result was statistically significant.

The Michigan cohort study evaluated seven measures of sustained attention and working memory in 4-year-old study participants (Jacobson et al. 1992; Jacobson and Jacobson 2003) with variable results depending on the specific test or subtest, or population subgroup. Two subscales of the Continuous Performance Test (CPT) – "percent correct" and "errors of commission" were also evaluated in the Oswego, NY cohort (Stewart et al. 2003a). Despite similar tests, the results of two studies cannot be compared because exposure in the Michigan cohort analyses was expressed as non-specified PCB concentration in child's blood or as a composite measure of breast milk and maternal and cord blood levels, whereas the Oswego cohort only presented data for cord blood PCBs. This lack of consistent reporting is surprising because the Michigan cohort (Jacobson et al. 1992) had data on cord blood levels.

In summary, the preschool age group included studies that could have examined as many 21,280 associations. Yet, as study participants got older the proportion of associations that were addressed in two of more cohorts became vanishingly small, just 0.1% (11 results). Of those 11 results, two were consistently non-significant and nine were conflicting; none of the significant results were replicated.

School age (6 years or older)

As the participants of the cohort studies entered school age, the number of publications evaluating various associations between PCB exposure and neurodevelopmental test results increased further. To date, the available body of literature in this category of studies includes results from 18 different cohorts (Berghuis et al. 2018; Boucher et al. 2010; Boucher et al. 2012a; Boucher et al. 2012b; Boucher et al. 2016; Ethier et al. 2012; Ethier et al. 2015; Forns et al. 2012b; Gladen and Rogan 1991; Grandjean et al. 1997; Grandjean et al. 2001; Grandjean et al. 2012; Gray et al. 2005; Hoyer et al. 2015; Jacobson and Jacobson 1996, 2002a, b, 2003; Jacobson et al. 2015; Kostiakova et al. 2016; Longnecker et al. 2004; Murata et al. 2004; Neugebauer et al. 2015; Nowack et al. 2015; Orenstein et al. 2014; Palkovicova Murinova et al. 2016; Rosenquist et al. 2017; Sagiv et al. 2010; Sagiv et al. 2012; Sioen et al. 2013; Stewart et al. 2005; Stewart et al. 2006; Stewart et al. 2008; Stewart et al. 2012; Verner et al. 2010; Verner et al. 2015; Vreugdenhil et al. 2002a; Vreugdenhil et al. 2002b; Vreugdenhil et al. 2004a; Vreugdenhil et al. 2004b; Vuong et al. 2017; Winneke et al. 2005; Winneke et al. 2014; Zhang et al. 2017).

Despite numerous analyses conducted across multiple cohorts, the number of neurodevelopmental measures addressed by at least two groups of investigators is small. Seven cohort studies (Michigan, Oswego, CPP, New Bedford, Nunavik, Northern Netherlands and the Faroe Islands) administered the Wechsler Intelligence Test for Children (WISC), which is typically expressed as a full scale IQ, as well as Verbal and Performance IQ scores. The three IQ scores are based on a wide range of individual scales (e.g., arithmetic, verbal comprehension, digit span, block design, etc.)

In the Michigan cohort, WISC results at 11 years of age were evaluated in relation to three types of PCB exposure: concentrations of non-specified congeners in child's blood samples at the time of testing; cumulative intake via breast milk, and a composite measure based on levels in cord blood, maternal blood and breast milk (Jacobson and Jacobson 1996, 2002a, b, 2003). No significant associations were observed with any of the postnatal measures of PCB exposure. For the composite perinatal measure the authors reported a statistically significant inverse association with Full Scale IQ, and Verbal IQ, but not Performance IQ (Jacobson and Jacobson 1996). Further analyses of WISC results in relation to composite perinatal measure of PCB exposure demonstrated that the results differed depending on the study subgroup, but these results were not reported consistently. For example, the authors reported that full scale IQ was inversely associated with perinatal PCBs among children who were breastfed for less than 6 weeks, but the corresponding information is not provided for Verbal and Performance IQ scores (Jacobson and Jacobson 2002a, b). Similar associations with individual sub-scale components are reported for Arithmetic and Digit Span in one publication (Jacobson and Jacobson 2003) while the other papers (Jacobson and Jacobson 1996, 2002a, b) focused on Verbal Comprehension, Perceptual Organization and Freedom from Distractibility.

The Oswego cohort examined WISC results at 9 and 11 years of age in relation to cord blood and placental tissue PCBs (Stewart et al. 2008; Stewart et al. 2012). None of the results for cord blood levels were significantly different from the null. The associations with total placental PCB levels were statistically significant for Full Scale IQ, Verbal IQ and Freedom from Distractibility subscale at 9 years of age (Stewart et al. 2008). When the same analyses were repeated at 11 years of age, after controlling for covariates and co-exposure with hexachlorobenzene, the Full Scale and Verbal IQs were no longer significantly associated with placental PCBs, however the association with Freedom from Distractibility subscale remained significant (Stewart et al. 2012).

The New Bedford, Massachusetts study (Sagiv et al. 2012) evaluated two subsets of the WISC – Processing Speed and Freedom from Distractibility, each examined in relation to two exposure measures: the sum of four PCB congeners (118, 138, 150 and 180) and the computed TEQ for the sum of the five dioxin-like mono-ortho PCB congeners (105, 118, 156, 167, and 189). The results for Processing Speed were mixed with inverse associations observed for boys, but not for girls and not for all children examined together. The results for Freedom from Distractibility were not statistically significant regardless of exposure measure across all groups of participants.

The CPP cohort (Gray et al. 2005) conducted WISC assessment at 7 years of age and reported no statistically significant inverse associations between maternal blood PCBs and any of the IQ measures. Unlike the Michigan study, there was no evidence that the association was modified by breastfeeding duration.

Children enrolled in the Nunavik cohort study underwent WISC testing at the age of 11 years (Jacobson et al. 2015). Only full IQ results were reported. No association was observed with PCB-153 levels in either cord blood or child's blood samples.

Another study evaluating the association between PCBs and full IQ based on WISC testing examined 8-year children enrolled in the Health Outcomes and Measures of the Environment

(HOME) Study, a birth cohort in Cincinnati, Ohio (Zhang et al. 2017). Although the authors reported measuring 36 PCB congeners the data were only presented for one exposure – the sum of PCB-118, -153, -138/158, and -180. No association between PCB and IQ was observed (Zhang et al. 2017).

The children enrolled in the Northern Netherlands cohorts underwent WISC testing at the age of 13-15 years (Berghuis et al. 2018). Exposure assessment included 18 different maternal blood measures: six hydroxylated PCBs (4-OH-PCB-107, 4-OH-PCB-146, 3-OH-PCB-138, 3-OH-PCB-153, 4-OH-PCB-172, and 4-OH-PCB-187), ten congeners (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and two combined measures. Each of the 54 associations was examined using linear and logistic regression models. Several linear regression results for Total and Verbal IQ were statistically significant, all in the opposite of the hypothesized direction. One of the logistic regression results (for PCB-183 and Total IQ) was significant in the hypothesized direction, but only in the crude and not in the adjusted model (Berghuis et al. 2018).

The Faroe Islands cohort also administered WISC at the age of 7 years, but only reported using three of its specific components – Digit Span, Similarities and Block Design (Grandjean et al. 2001; Grandjean et al. 2012). The study used 17 different PCB metrics reflecting various individual congeners and combinations of congeners in cord blood, cord tissue, and blood samples obtained from participants at the time of testing. Only one of the associations (between PCB-138 in cord blood and Block Design test) was statistically significant (Grandjean et al. 2012).

A version of the WISC test, called Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) was administered in the Eastern Slovakia birth cohort when the participants were 6 years of age (Drobna et al. 2019). The specific test components used in the analyses included eight measures: Block design, Information, Matrix reasoning, Vocabulary, Picture concept, Symbol search, Word reasoning, and Coding as well as the Composite score. Each of these measures was examined in relation to levels of PCB-118 and PCB-153 in blood samples of children obtained at the time of testing. The authors reported "PCB-153 and PCB-118 were not statistically significantly associated with WPPSI-III in any of investigated models." (Drobna et al. 2019)

Five cohort studies reported different components of the Continuous Performance Test, which is designed to examine attention and evaluates a variety of parameters including reaction time, total number of correct or erroneous responses, and specifically errors of commission and errors of omission. In the Michigan cohort (Jacobson and Jacobson 2003) the composite measure of perinatal exposure was not related to reaction time or total number of correct responses. The association with errors of commission was statistically significant, but only among children who were breastfed for less than 6 weeks. In the Oswego cohort (Stewart et al. 2005) the association with errors of commission among children between 8.5 and 9 years of age was statistically significant, but only when exposure was expressed as sum of C17-C19 congeners in cord blood. There was no association with the number of correct responses whereas data for reaction time were not presented. Children enrolled in the Spanish INMA cohort underwent Continuous Performance Test at the age of 11 years (Forns et al. 2012b). No significant associations were observed with cord blood PCBs. When data analysis was conducted in relation to PCB levels measured in blood samples drawn at 4 years of age there were no significant associations for

either errors of commission or errors of omission. The reaction time was significantly delayed in children who had higher PCB levels at age 4, but this association was no longer evident after controlling for birth weight and exposure dichlorodiphenyl dichloroethylene. Reaction time on the Continuous Performance Test was also evaluated in the New Bedford, Massachusetts cohort at age 8 years (Sagiv et al. 2012). The data were presented separately for the sum of PCB-118, 138, 153 and 180 and for the total TEQ of mono ortho congeners in cord blood. The results for both exposure measures demonstrated significantly shorter (i.e., better) reaction time in girls with higher PCB levels and no association in boys. By contrast, the errors of omission rate was increased in relation to higher mono ortho PCBs, but only among boys.

A more recent study of children enrolled in the HOME cohort evaluated the association between the sum of not specified PCBs (15 congeners) measured in maternal blood and Continuous Performance Test at 8 years of age (Vuong et al. 2017). The dependent variables in that study included several Continuous Performance Test-derived indices, including errors of omission, errors of commission, reaction time and tau (τ), the exponential component of the reaction time distribution. The results for PCBs were presented for only two of those indices – errors of omission and tau; both demonstrated no discernible association (Vuong et al. 2017).

In the Faroe Islands cohort (Grandjean et al. 2001; Grandjean et al. 2012) reaction time at 7 years of age was not related to cord tissue or cord blood PCBs, whereas errors of commission were not presented. For errors of omission the only significant association was observed for one congener – PCB-118 in cord blood (Grandjean et al. 2012), but it is important to keep in mind that this association was not adjusted for mercury exposure. It is likely that adjusting for mercury levels would have changed the results because this happened in all analyses that controlled for mercury exposure.

The Faroe Island investigators observed a statistically significant association between sum of wet-weight (but not lipid adjusted) cord tissue PCBs and higher hearing thresholds at one high (1200 Hz) and one low (250 Hz) frequency (Grandjean et al. 2001). Although these results represented only two out of 72 possible associations, they motivated confirmatory analyses of the data from the CPP cohort (Longnecker et al. 2004). The CPP investigators analyzed the data using 96 different methods and reported them all. There was only one statistically significant association – a higher hearing threshold at 4000 Hz in the right ear in relation to higher lipid-adjusted maternal PCBs (Longnecker et al. 2004).

One additional measure – Finger Tapping Test – was examined in more than one study. During the Finger Tapping Test administration, the child is asked to tap a key as fast as possible for 15 seconds, first using the dominant hand and then using the non-dominant hand. The results for each hand are then combined to calculate the overall score. The previously discussed Faroe Islands studies (Grandjean et al. 2001; Grandjean et al. 2012) observed no evidence of an association of Finger Tapping Test results at 7 years of age with any of the PCB exposure metrics. By contrast, the Nunavik cohort investigators reported a statistically significant association between test result at the age of 11 years (both hands) and current blood levels of PCB-118, 138, and 180 as well as the sum of all congeners. There was no evidence of an association between Finger Tapping results and cord blood PCBs after controlling for confounders (Boucher et al. 2016).

A behavioral test – Pre-School Activity Inventory (PSAI) – offers an additional opportunity to examine inter-cohort consistency. It was used in the Rotterdam and the Duisburg studies. The PSAI is administered to parents and is designed to distinguish between feminine and masculine play behavior, each assigned a separate score; in addition, a composite score is calculated as the difference between the feminine and the masculine scale results. The Rotterdam cohort investigators reported results for each PSAI score in relation to the sum of maternal and cord blood PCBs (118, 138, 153 and 180) as well as various measures of PCB intake via breast milk (Vreugdenhil et al. 2002b). Exposure through lactation was not related to masculine or feminine play behavior in any of the analyses, although the association with composite score was significant and inverse in girls but not in boys. In the analyses for cord and maternal blood PCBs masculine play was significantly reduced in boys, but the corresponding result was in the opposite direction and not significant in girls (Vreugdenhil et al. 2002b). The findings from the Duisburg cohort study (Winneke et al. 2014) were almost exactly the opposite, although the two sets of results cannot be compared directly due to the differences in exposure assessment. In the analyses of the masculine score in relation to maternal blood or breast milk PCBs (each expressed as a sum of dioxin-like TEQs), only the result for breast milk levels was significant, indicating lower masculine play in girls but higher (albeit non-significant) in boys. The corresponding results for feminine score were also positive in boys and inverse in girls; all associations with breast milk measures were statistically significant, while the associations with maternal blood PCBs were only significant in boys. Unlike the Rotterdam study (Vreugdenhil et al. 2002b), none of the analyses for the composite PSAI score in the Duisburg cohort were statistically significant (Winneke et al. 2014).

In summary, of the 25,116 possible associations in the school-age cohorts, only 69 (0.3%), were evaluated and reported by two or more groups of investigators. Of those, 65 results were consistently non-significant and four were conflicting.

Summary

The existing body of literature examined 261 exposure metrics and 459 different neurodevelopmental measures (see **Appendices I and II**). As shown in **Figure 1** (p. 84), this created an opportunity to examine 119,799 different associations. It is therefore not surprising that many articles included in the present review were in a position to report at least some positive findings. Yet, very few studies addressed the same or similar specific research questions. It is not realistic to expect that all 35 cohorts would examine the same associations; however, the proportion of associations examined in at least two different cohorts was vanishingly small (about 0.1%). Of those, most (76%) were consistently non-significant or, if significant, in the direction opposite of the expectation, and 24% were conflicting (represented a combination of statistically significant and non-significant/opposite or mixed results), and none demonstrated a complete agreement in terms of finding a statistically significant association in the hypothesized direction.

Some of the postnatal PCB measures may have been obtained later in life and could not precede the tests administered at younger ages. Therefore, to assure temporality, in a separate analysis, I restricted exposures to those measured prenatally or within the first month of life. As shown in **Figure 2** (p. 85), this restriction did not change the results.

DO THE SAME PCB EXPOSURES PRODUCE EFFECTS AS CHILDREN GROW OLDER?

This question is related to intra-cohort consistency, which can be defined as "…observing similar exposure-outcome associations… within the same population" (Burns et al. 2013). Several cohorts considered in the current report were examined only once. For this reason the following sections are limited to study populations that underwent two or more assessments at different ages during follow up, and offer an opportunity to evaluate intra-cohort consistency over time.

Michigan cohort

The Michigan cohort included 313 mothers and their newborn children; 242 women reported "moderate consumption of Lake Michigan fish" and 71 had no such exposure (Jacobson et al. 1984a). The mother-child pairs were recruited in Western Michigan counties that were known as sites of the 1973 accident associated with contamination of polybrominated biphenyls (Jacobson et al. 1984b).

In the newborn period the focus of the data analyses was on fish consumption as a measure of PCB exposure and its relation to NBAS test scores. Although the results were internally not consistent, the authors concluded that "contaminated fish consumption predicted motoric immaturity, poorer lability of states, a greater amount of startle, and more abnormally weak (hypoactive) reflexes" The authors also indicated that cord serum PCB levels did not "predict a linear combination of NBAS clusters". The authors attributed this finding to the limitation of their data because cord serum PCB levels were not available for 36.7% of the participants and because these values were more likely to be missing among fish-exposed cohort members.

The next opportunity to evaluate the Michigan cohort was presented at the ages of 5 and 7 months. The analysis at 7 months of age was published first (Jacobson et al. 1985); it focused on FTII and included only 123 infants. This represented 39% of the original study group (N=313). The data on cord blood PCB were limited to just 81 participants "due to technical problems in laboratory analysis". Breast milk samples were available for 67 of 88 nursing mothers. It is not clear what proportion of mothers in the total cohort (N=313) were breastfeeding although in one of the later publications that number was reported to be 172 (Jacobson et al. 1990). There was a statistically significant inverse association with FTII novelty scores for the first two (fish intake and cord blood PCB) of the three exposure measures.

The second study evaluating 5-month-old members of the Michigan cohort focused on BSID results (Jacobson et al. 1986). No information about the numbers of participants or numerical results are provided. The authors only state that none of the measures of prenatal PCB exposure were related to either MDI or PDI, whereas the corresponding results for breast milk PCB are not mentioned at all.

The Michigan cohort was again re-evaluated at 4 years of age. The first publication reporting results of the 4-year follow up was based on cord blood and breast milk PCB levels available for 146 and 120 children, respectively (Jacobson et al. 1990). The study found statistically significant inverse associations between total cord blood PCBs and Verbal and Memory subscales of MSCA, but not for GCI or for any other subscales. There was also no association

between cord blood PCBs and two other measures – Visual-Motor Impairment test and Peabody Picture Vocabulary Test-Revised. The analyses of breast milk data are only reported for two MSCA components – Memory and Quantitative; the former showing a statistically significant association and the latter yielding a non-significant result.

The second publication that evaluated children at 4 years of age was published two years later (Jacobson et al. 1992) and administered a wide range of tests aimed at assessing cognitive processing efficiency (short-term memory) and sustained attention. The reported neurodevelopmental measures included four components of the Sternberg Memory Test (Reaction Time, Number Correct, Total Errors, and Errors of Commission) two components of Visual Discrimination Test (Reaction Time and Number Correct) and a composite score of the Vigilance Test (which also includes Reaction Time, and various measures of correct and erroneous responses). The number of children that underwent evaluation ranged from 199 to 224, depending on the test; in the Methods section, the authors state that cord serum data were available for 143 children, but the statistical analyses appear to be limited to 132 participants. It is not clear how many participants were included in the analyses of the association with breast milk PCBs, although the number of samples was reported to be 118. There was no internal consistency across findings. The cord blood PCBs were found to be associated with short-term memory errors on the Sternberg tests whereas breast milk PCB levels were related to Visual Discrimination.

It is important to point out that fish consumption, which was one of the central exposure metrics in previous articles (Jacobson et al. 1984a; Jacobson et al. 1985; Jacobson et al. 1986) is no longer examined in the subsequent publications. This is surprising because fish exposure was ascertained in the majority of participants, and would have been less affected by loss of data.

Three additional publications examined various neurodevelopmental measures at 4 years of age using a composite PCB exposure measure "derived by averaging the cord serum, maternal serum, and breast milk measures using only values above the detection limit." (Jacobson and Jacobson 2002a, b, 2003). As described elsewhere (Jacobson and Jacobson 1997), all three measures were converted to z-scores and all values below the detection limit (67% and 23% of cord and maternal blood samples, respectively) were excluded from the analyses. No data are available on how these exclusions may have affected the observed associations.

The first two publications examined the association between composite measure and MSCA results among 181 children who "cooperated with the 4-year testing" (Jacobson and Jacobson 2002a) Unlike the earlier study (Jacobson et al. 1990), in the 2002 publications, the authors found that higher composite PCB exposure levels were associated with lower CGI and Quantitative Performance as well as Verbal and Memory scores, but not in certain subgroups of children such as those who were breastfed for at least 6 weeks or those whose mothers scored at least 89 points on the Peabody Vocabulary test (Jacobson and Jacobson 2002a, b).

The third publication evaluating composite PCB exposure used various tests of attention and information processing as the measures of interest (Jacobson and Jacobson 2003). Although the age of assessment and domains of interest were the same in this and in the previous study (Jacobson et al. 1992) only one test (Sternberg Memory) was reported in both publications. Unlike the earlier report, no data on Visual Discrimination Task and the Vigilance Test (both

supposed to measure sustained attention) were included; instead the association between composite PCB exposure and sustained attention was examined using Continuous Performance Test (CPT) among 154 children. The reporting for the Sternberg Memory Test also differed in the two studies; the results for total errors (shown to be associated with cord blood PCB in the 1992 publication) were no longer presented in the 2003 paper. Instead the focus of the new analysis was on errors of commission (which were not associated with PCBs in the previous paper).

When the same cohort was again evaluated at 11 years of age the data for Sternberg Memory Test were only presented for Reaction Time and Total Correct. Unlike the same analyses for the age of 4 years in the same publication (Jacobson and Jacobson 2003), no results are available for Errors of Commission or Total Errors. Evaluation at 11 years of age also included a wide array of tests and subtests, most of which were never reported previously or since (Jacobson and Jacobson 2002a, b, 2003). The numbers of participants in the analyses assessing the association between these neurodevelopmental tests and various measures of exposure ranged from 145 to 178 (depending on the test). The association of each neurodevelopmental measure with composite PCB exposure estimate was presented using a variety of metrics, but importantly, the significant associations were usually limited to certain subsets of children (Jacobson and Jacobson 2002a, b, 2003). For example, the results for the Woodcock Word Comprehension test were statistically significant only among children who were breastfed for less than 6 weeks, whereas Mental Rotation test was significantly associated with the composite PCB measure in children who were breastfed for 6 weeks or longer. Similarly, the Perceptual Organization score of the WISC test was only significantly associated with PCBs in children whose mothers scored at least 89 points on the Peabody Vocabulary test, while Freedom from Distractibility score results were only significant in children whose mothers received a Peabody Vocabulary score of less than 89. The authors interpreted these differences as evidence that certain subgroups of children may be more vulnerable to the effects of prenatal PCB exposure; however an alternative, and more likely explanation is that these findings are attributable to differential loss to follow up, non-randomly missing exposure information, excessive stratification of the data, and *a posteriori* decisions on which analyses should be presented.

North Carolina cohort

The North Carolina cohort study was coordinated by the National Institute of Environmental Health Sciences and enrolled pregnant women from "hospital familiarization tours," Lamaze classes, and private and public prenatal clinics. Sample collection involved breast milk, colostrum or formula as well as blood from the mother, cord blood, and placenta (Rogan et al. 1986a).

The earliest publication from the North Carolina cohort examined the association between PCB levels in breast milk or colostrum fat at birth and NBAS test results among 866 newborns (Rogan et al. 1986b). The prenatal PCB exposure in that study was assessed based on estimated concentrations in breast milk fat at birth. While the authors reported that higher PCB exposures were associated with NBAS motor (a.k.a. tonicity) and reflex clusters these conclusions are not completely supported by the statistical analyses because none of the p-values calculated based on the numbers provided in Tables 1 and 2 of that publication approached statistical significance.

Two subsequent publications (Gladen et al. 1988; Rogan and Gladen 1991) reexamined participants in the North Carolina study at 6, 12, 18 and 24 months of age using BSID as the neurodevelopmental test of interest. The 6 and 12-month assessment included 802 (93% of the original cohort) infants and produced a statistically significant inverse association between PDI and composite measure of PCBs in maternal blood, cord blood, placenta and breastmilk (standardized to breast milk fat levels close to birth). The results for MDI demonstrated no association at either age. When BSID was again administered at 18 and 24 months of age to 676 and 670 children (78% and 77% of the original cohort, respectively) the association with PDI was not established (Rogan and Gladen 1991). The authors asserted that the result at 24 months of age was significant; however, a closer inspection of the data indicates that the confidence intervals around the differences between the lowest exposure category and all subsequent categories (including the highest) overlapped the null value; although the result may have been significant based on the ANOVA test. Once again no associations were observed for MDI.

At ages 3, 4 and 5 years the North Carolina children were again examined using MSCA (Gladen and Rogan 1991). Test scores were obtained from 645 children (74% of 866 participants) at 3 years, 628 (73%) at 4 years, and 636 (73%) at 5 years of age. Nether exposure metric was associated with any of the MSCA scores. The same publication also evaluated the association between PCB exposure and school performance from the 3rd to the 5th grade. At least one report card was available for 506 children (58%). No associations with either English or mathematics grades were observed.

Oswego, NY cohort

The Oswego cohort is described as "the first large scale replication and extension" of the Michigan cohort (Lonky et al. 1996). Pregnant women were recruited for this study at the time of the 20-week prenatal ultrasound visit. Of the 2,587 women eligible for the study 1,337 (52%) agreed to be interviewed; however, the initial reports of neurodevelopmental measures in relation to various measures of exposure were based on 559 subjects in the analysis of fish intake (Lonky et al. 1996) and 293 subjects in the analysis of cord blood PCBs (Stewart et al. 2000). The cord blood PCBs were characterized as total, lightly chlorinated (C11-C13), moderately chlorinated (C14-C16), and highly chlorinated (C17-C19). Unlike the previous study (Lonky et al. 1996), which defined the dependent variable as the difference between the scores of the NBAS test administered on the 1st and 2nd days of life, the quantitative results in the Stewart et al. (2000) publication were reported only for the second assessment. The authors do mention that none of the measures were associated with NBAS administered on the first day of life, but provide no numerical results. Two of the seven clusters (range of states and autonomic maturity) recorded on the second day of life were associated with PCB exposure, but only when the analyses were limited to C17-C19 compounds. The results for total PCBs are not mentioned, and for other compounds the authors only state that lightly or moderately chlorinated PCBs were "not related to habituation, autonomic or abnormal reflex clusters."

When a subset of the same cohort (N=230) was re-evaluated at 6 months of age using FTII there was a statistically significant association with total, but not C17-C19 PCBs, but later at the age of 12 months (N=219) the same study reported a significant association with C17-C19 but not total PCBs (Darvill et al. 2000). The numerical results for fish consumption were no longer reported

at either 6 or 12 months of age; however in the Discussion section the authors state the their analyses for FTII "revealed no significant effect of maternal fish consumption"

The association with fish consumption was mentioned again when 194 and 197 participants underwent MSCA evaluation at 3 and 4.5 years of age, respectively; no numeric results were provided, but the authors state that "no relationship was observed." (Stewart et al. 2003b). Unlike previous analysis, the results for total cord blood PCBs are also not reported; instead, the focus of the analysis is on C17-19 congeners, which were found to be associated with some MSCA subscales at 3, but not at 4.5 years of age (Stewart et al. 2003b). It is important to point out that in more than half of cord blood samples (173 of 293 or 59%) levels of C17-C19 PCBs were below the limit of detection. Another publication (Stewart et al. 2003a) reported results for two components of the CPT – "percent correct" and "errors of commission". The number of participants in that study further decreased to 189 and the exposure was limited to C17-C19 PCBs in cord blood. The authors assert a "dose-dependent association between cord blood PCBs and errors of commission"; however this conclusion is only applicable to certain sub-analyses as evidenced in various interactions between exposure and seemingly unrelated factors such as testing block number or splenium size of the corpus callosum. No association was observed for percent correct and no information is available for other CPT components such as errors of omission or reaction time.

The more recent evaluation of the Oswego cohort occurred between the ages of 8 and 9.5 years. The first publication in the series also focused on CPT and reported a significant association between percent correct and cord blood C17-C19 PCBs (Stewart et al. 2005). The previously observed interaction between C17-C19 PCBs and testing block number was no longer present, and no data were reported on the previously observed interaction with splenium size of the corpus callosum. In the second publication (Stewart et al. 2006) the neurodevelopmental measure of interest was the Differential Reinforcement of Low Rates (DRL) task which included inter-response times (IRT) and total reinforced responses (TRR). Unlike several previous publications that focused exclusively on C17-19 congeners, the 2006 study again included total PCBs data in addition to C17-C19 PCBs in cord blood. Total PCBs were associated with both IRT and TRR DRL components, whereas the association with C17-C19 PCB was only present for IRT. The two more recent Oswego cohort publications (Stewart et al. 2008; Stewart et al. 2012) focused on WISC results at the age of 9 years. No associations were observed with cord blood PCBs but these results are only mentioned briefly in the text (Stewart et al. 2008). Instead, the authors focused on a different type of sample – placental tissue, and "total PCB" variable was comprised primarily of 118, 138, 153 and 180 congeners. Recall that lightly chlorinated (C11-C13) PCBs (including 118 and 138 congeners), and moderately chlorinated (C14-C16) PCBs (including 153 congener) in cord blood were found to be not associated with any of the neurodevelopmental measures in the neonatal period (Stewart et al. 2000) and were no longer presented in any of the subsequent analyses. At 9 years of age (N=154) the associations with total placental PCB levels were statistically significant for Full Scale IQ, Verbal IQ and Freedom from Distractibility (Stewart et al. 2008) although in a more recent re-analysis (Stewart et al. 2012), after controlling for hexachlorobenzene (HCB) co-exposure, the association with Full Scale IQ was no longer significantly different from the null. When the same analyses were repeated at 11 years of age (N=145), after controlling for covariates and co-exposure with HCB, only the association with Freedom from Distractibility subscale remained statistically significant (Stewart et al. 2012). The authors then conducted additional analyses using either data from the

9-year or the 11-year assessment or a mean of both values (N=158). The rationale for conducting the analyses this way, rather than by using more commonly accepted longitudinal models is not given.

Collaborative Perinatal Project cohort

The Collaborative Perinatal Project (CPP) was a multicenter cohort study that recruited participants from eleven US cities (Daniels et al. 2003). The study followed growth and development of approximately 44,000 US children born in 1959 through 1966.

All participants underwent BSID testing at the age of 8 month and all had prenatal maternal blood samples available. Approximately 71% of children were followed to the age of 7 years. The evaluations conducted during follow up included the Stanford-Binet IQ test administered at the age of 4 years, and both WISC and the Wide Range Achievement Test (WRAT) administered at the age of 7 years.

For each analysis of the association between PCBs and test results, participants were selected at random from the overall group and separately (also at random) from a subgroup of cohort members who had "extreme test" results, i.e., those who scored one standard deviation above or below the cohort average (Daniels et al. 2003; Gray et al. 2005). The analyses used weighted models to account for this sampling approach. Exposure in individuals selected for each data analysis was ascertained based on 11 PCB congeners (8, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) measured in maternal blood samples collected in the third trimester. The same exposure measure was used throughout the follow up.

The first analysis evaluated the association between prenatal PCB exposure and BSID results at 8 months of age and included 1065 children from the overall study population and 194 children from the "extreme results" group. There was no association between BSID (MDI or PDI) and any of the PCBs examined individually or in combination (Daniels et al. 2003).

The next publication conducted similar analyses based on 1,256 subjects randomly selected at the age of 7 years from the overall study group and an additional 207 children selected among those with "extreme" WISC IQ scores (Gray et al. 2005). The same participants also provided data for the analyses focusing on WRAT and on Stanford-Binet scores at the age of 4 years. After exclusion of participants with missing values for covariates of interest, the final models were limited to 894 subjects (61% of the sample).

The association between sum of PCBs and Stanford-Binet IQ at 4 years of age was statistically significant, but in the opposite of the hypothesized direction (i.e., children with higher prenatal exposure to PCBs had significantly higher IQs relative to children with lower PCB exposure levels). None of the associations with WISC IQ, WRAT or any of their components were statistically significantly different from the null. There was no evidence of significant interaction with any of the covariates, including breastfeeding (Gray et al. 2005).

One additional analysis of the CPP cohort data examined the association between PCBs and sensorineural hearing function at the age of 8 years (Longnecker et al. 2004). Among 1200 subjects selected at random from the overall cohort 726 had audiometric evaluation results by the

age of 8 years. In addition 220 children were selected from among 440 participants who had evidence of sensorineural hearing loss. The study included 96 statistical analyses: 6 different frequencies (250-8000 Hz) for each ear, with 8 different exposure metrics. There was only one statistically significant association – a higher hearing threshold at 4000 Hz in the right ear in relation to higher lipid- and batch-adjusted PCBs (Longnecker et al. 2004).

Dutch cohorts (Rotterdam, Rotterdam-Groningen and Northern Netherlands)

The Dutch cohorts were assembled in two different areas: Groningen, a semi-urban region in the Northeast, and Rotterdam, a major metropolitan area in the Southwest. The Rotterdam cohort was sometimes analyzed separately, whereas data on children in the Groningen cohort were always examined together with the data from Rotterdam. The two cohorts recruited 418 pregnant women across two sites with the aim of including half of those who intended to nurse their children and half of those who planned to use formula.

The first evaluation of the Rotterdam-Groningen cohort measured four congeners (118, 138, 153 and 180) in maternal and cord blood and 26 congeners in breast milk (Huisman et al. 1995a). The main neurodevelopmental measure of interest was NOS. The results were reported for the overall NOS and for two components; reflexes and muscle tone. There were statistically significant associations with several PCB congeners in breast milk, but not in cord blood or maternal blood samples.

At the age of 3, 7 and 18 months members the Rotterdam (but not Groningen) cohort underwent BSID testing; this study included 207 subjects, although the number of children with available test results varied by age (Koopman-Esseboom et al. 1996). Exposure was categorized as a sum of PCB-118, 138, 153, 180 in breastmilk, and in cord blood and maternal blood samples. Only maternal blood concentration was found to be associated with one BSID component (PDI) and only at 3 months of age. No statistically significant association with either exposure measure was observed at 7 or 18 months of age.

Both Rotterdam and Groningen study participants (N=373) were re-examined using NOS at 18 months of age (Huisman et al. 1995b). Unlike the earlier study (Huisman et al. 1995a) there was no association with breastmilk PCBs. Cord blood and maternal blood PCB were associated with lower NOS but only in children whose fathers were non-smokers and not in those whose fathers smoked (Huisman et al. 1995b).

The next evaluation of the Rotterdam/Groningen cohort took place when the children (N=384) were 3.5 years of age (Patandin et al. 1999). This study used KAB-C as the test of interest. The results of KAB-C testing were statistically significantly associated with sum of PCBs (118, 138, 153 and 180 congeners) in maternal blood but only among children who were formula fed since birth. The associations with cord blood PCBs were similar (significant among formula fed children only), but these associations were only reported for one KAB-C component – simultaneous function; no results are available for the sequential functioning test or the overall KAB-C score. No significant associations were observed with PCBs in breastmilk or in child's blood samples. In addition to KAB-C, the assessment at 3.5 years of age included a Neurologic Optimality Score with specific focus on fluency of movements (Lanting et al. 1998). Exposure was characterized as sum of PCBs (118, 138, 153, 180) in maternal, cord or child's blood as well

various combinations of PCBs measured in terms of TEQ in breast milk. No significant associations were observed.

The Rotterdam-Groningen study participants underwent evaluation at the age of 6.5 years using MSCA (Vreugdenhil et al. 2002a). Among 372 children who remained in the cohort, no associations were present between lactational exposure to PCBs and any of the test results. In the corresponding analyses for maternal and cord blood PCBs, statistically significant associations were observed in some of the subgroups, but without a discernible pattern. For example, there were significant interactions between maternal blood PCB levels and maternal age and between cord blood levels and parental verbal IQ. By contrast, the differences between results for breast-fed and formula-fed groups, noted in the earlier study (Patandin et al. 1999) were not statistically significant.

The same group of authors also analyzed data limited to the Rotterdam cohort. At 7.5 years of age the children (N=158) were examined using the Pre-School Activity Inventory (PSAI) to assess play behavior (Vreugdenhil et al. 2002b). PSAI is a parent-completed questionnaire designed to assess masculine and feminine play behaviors, and the difference between the two expressed as a composite scale. None of the previously reported interactions were noted in this study. Instead, results differed by child's gender. For example, maternal and cord blood PCBs were associated with masculine scale in boys, but not girls, and breast milk PCBs were associated with composite scales in girls, but not boys.

The Rotterdam cohort was again assessed at the age of 9 years (n=83) with a wide range of tests, which included the Rey Complex Figure Test, the Simple Reaction Time Test, the Auditory–Verbal Learning Test and the Tower of London Test (Vreugdenhil et al. 2004a). Unlike earlier Rotterdam studies, only PCBs in maternal blood (sum of 118, 138, 153 and 180 congeners) were used to characterize exposure. Also unlike previous studies, exposure was simply dichotomized as high vs. low. In the overall analysis, high PCB exposure was significantly associated with Simple Reaction Time Test and the Tower of London test. The latter association was evident only in children who were formula fed or were breastfed for less than 17 weeks and not among children breastfed for at least 17 weeks. It is not clear if the same patterns were observed for other tests and for other exposure metrics, most notably cord blood PCBs.

In a separate publication (Vreugdenhil et al. 2004b), the 9-year-old Rotterdam cohort members (N=60) also underwent evaluation of auditory event-related potentials in response to stimuli. The test involved evaluation of two components (latency and amplitude) at three positions (frontal, central and parietal). Only maternal blood PCB levels were used to characterize prenatal exposure, which was again dichotomized as high vs. low. The results demonstrated statistically significant association of high PCB exposure to latency at central and parietal position, but not at frontal position. When stratified by breastfeeding status, the association with latency at parietal position was only evident in formula fed subjects. It is not clear if the same pattern was observed for latency at the other two positions. No associations were observed for amplitude measures. The authors also reported that lactational exposure was not related to test results.

The two more recent cohorts were assembled approximately 2 years apart among pregnant women receiving prenatal care in the Northern Netherlands. Enrollment in the first cohort

occurred between 1998 and 2000 as part of the Risk of Endocrine Contaminants (RENCO) study (Soechitram et al. 2004). The second cohort represented the Groningen site of the larger Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens (COMPARE) study; this cohort is often referred to as Groningen Infant COMPARE (GIC) study (Meijer et al. 2008)

The assessments of these cohorts at different ages were not necessarily published in chronological order. The RENCO cohort participants underwent extensive testing of neurologic function at 3 months age as described in two publications (Berghuis et al. 2013; Berghuis et al. 2014). In both publications exposure assessment included 18 different measures: six hydroxylated PCBs (4-OH-PCB-107, 4-OH-PCB-146, 3-OH-PCB-138, 3-OH-PCB-153, 4-OH-PCB-172, and 4-OH-PCB-187), ten congeners (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and the sums of hydroxylated and non-hydroxylated PCBs considered separately; however, the first publication (Berghuis et al. 2013) relied on cord blood analyses whereas the second publication (Berghuis et al. 2014) assessed PCB levels in maternal blood.

The first publication (Berghuis et al. 2013) focused on motor development ascertained based on video recordings and scored each aspect of motor function according to 13 different parameters. Unadjusted results produced several statistically significant associations, some in the hypothesized and some in the opposite direction. When the observed associations were examined using multivariable models (controlling for gender, gestational age and maternal smoking), only two results were statistically significant (in different directions): one showing an increased likelihood "absent antigravity movements" in relation to higher PCB-118 and another showing lower likelihood of "absent manipulation" in relation to higher 4-OH-PCB-172 (Berghuis et al. 2013).

The second publication assessing RENCO cohort members at 3 months (Berghuis et al. 2014) used neurologic optimality examination consisting of 53 items, which are subsequently organized into five clusters and combined into an overall Neurologic Optimality Score (NOS). The dependent variables in all analyses included the overall NOS and two clusters reflecting visuomotor and sensorimotor function. The results for each of the 18 exposure metrics were presented overall and separately for boys and girls. None of the analyses demonstrated a decrease in NOS with higher PCB exposures; however several measures of association demonstrated significantly better neurologic function with higher PCB levels in some of the analyses. Similarly in the analyses for visuomotor and sensorimotor clusters only one result was statistically significant in the hypothesized direction; whereas more than 30 measures of association demonstrated significantly better test results in children with higher maternal PCB levels. After controlling for confounding factors, none of the hypothesized associations were significant whereas some of the opposite associations remained (Berghuis et al. 2014)

The motor and mental development of children in both the RENCO and the GIC cohorts was assessed at 18 and 30 months of age using BSID (Ruel et al. 2019). Maternal blood measures included the same six hydroxylated PCBs (4-OH-PCB-107, 4-OH-PCB-146, 3-OH-PCB-138, 3-OH-PCB-153, 4-OH-PCB-172, and 4-OH-PCB-187), ten non-hydroxylated congeners (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and four combined measures (all 6 OH-PCBs, all 10 PCB congeners; dioxin-like PCBs 105, 118 and 156 and non-dioxin like PCBs 138, 146, 153, 170, 180, 183, and 187). Each of the twenty exposure metrics was examined in relation to MDI

and PDI at 18 and 30 months of age and presented as crude and (in some instances) adjusted measures of association. In addition, the results were sometimes presented separately for each of the two cohorts. Nearly all of these results showed no association. Only one adjusted result – for MDI and PCB-153 was statistically significant. This association was present only at the age of 18 months but not at 30 months of age, and only in the GIC cohort, but not in the RENCO study population (Berghuis et al. 2014).

Children enrolled in the GIC cohort were evaluated between 5 and 6 years of age (Roze et al. 2009) using a wide range of tests assessing motor development, cognitive function and behavioral problems. Each neurodevelopmental and behavioral measure was examined in relation to maternal blood level of PCB-153, and three hydroxylated compounds - 4-OH-PCB-107, 4-OH-PCB-146, and 4-OH-PCB-187. Most results were not statistically significant and therefore were not included in any of the tables. Among those results that were reported, relatively few statistically significant associations were observed in either direction; and there was no identifiable pattern.

In a more recent study, the children enrolled in both Northern Netherlands cohorts underwent intelligence, verbal memory, attention and motor skills testing at the age of 13-15 years (Berghuis et al. 2018). A total of 12 different measures were examined in relation to 18 different maternal blood measures: six hydroxylated PCBs (4-OH-PCB-107, 4-OH-PCB-146, 3-OH-PCB-138, 3-OH-PCB-153, 4-OH-PCB-172, and 4-OH-PCB-187), ten congeners (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) and two combined measures. Once again most associations were not included in the tables because they were not "significantly or marginally significantly related to cognitive and motor outcome" (Berghuis et al. 2018). In the adjusted analyses only two results were statistically significant, both in the opposite of the hypothesized direction (Berghuis et al. 2018). .

Nunavik cohorts

Nunavik, an area in Northern Quebec, Canada was the site of two different studies. The first study included children who were born between 1993 and 1998 and whose cord blood samples were collected as part of the Arctic Cord Blood Monitoring Program (Boucher et al. 2010; Boucher et al. 2012a; Boucher et al. 2012b; Boucher et al. 2016; Despres et al. 2005; Ethier et al. 2012; Saint-Amour et al. 2006). The second study included 94 children whose mothers were invited to participate during pregnancy between 1995 and 2001 (Boucher et al. 2014). It is not clear if the populations of the two cohorts overlap.

The first cohort examined participants between the ages of 4 and 6 years and evaluated their neuromotor function. The study assessed associations of 29 exposures representing various PCB congeners and congener combinations in cord blood and child's blood sample with 11 different neurodevelopmental measures reported as correlations and linear regression coefficients. Only one of those results (a regression coefficient reflecting the association between child's blood PCB-153 and a specific measure of sway) was statistically significant (Despres et al. 2005).

Another study of the same cohort at the same age (Saint-Amour et al. 2006) focused on only one congener PCB-153 in child's blood samples and evaluated 15 different measures of visual evoked potentials latency and amplitude. Unlike the first study (Despres et al. 2005) no data on

other congeners or on cord blood measures are reported. The study observed 3 statistically significant regression coefficients without a discernible pattern.

At the age of 5 years the Nunavik study participants underwent a behavioral assessment using the Infant Behavior Rating Scale, which includes several components reflecting social ease, cooperation, emotional tone, activity, attention, impulsivity, anxiety and irritability (Plusquellec et al. 2010). In addition, the investigators videotaped the assessment of fine motor function and summarized the observations using seven different indicators: off task latency, global activity rate, global activity latency, vocalization, positive affect rate, off task duration, and legs activity duration. Each behavioral measure was examined in relation to cord blood and child's blood PCB-153. Only some of the 30 possible associations with PCB-153 are reported in the article: three (emotional tone, anxiety and positive affect rate) were statistically significant for cord blood concentration and one (global activity latency) was significant for child's blood level (Plusquellec et al. 2010).

The children in the first Nunavik cohort were re-examined at the age of 11 years. The assessment included a number of tests evaluating motor function, and event-related potentials in response to auditory and visual stimuli. The results were not internally consistent and were not reported in a coherent fashion. For example, fine motor function tests showed no association with cord blood PCBs, but some of the test results were associated with PCBs in child's blood (Boucher et al. 2016). The auditory evoked potentials were not associated with child's blood PCBs; however, they were associated with cord blood PCBs, but only in some analyses and only among children who breastfed for less than three months (Boucher et al. 2010). The visual evoked potentials were only examined in relation to one congener - PCB-153, with multivariable analyses demonstrating a statistically significant association for 3 out of 13 different test components in relation to child's blood, but not cord blood, levels (Boucher et al. 2012a). In another analysis also focusing on PCB-153 but in relation to a different set of visual evoked potentials tests (Ethier et al. 2012) the authors reported "no significant association was found for PCB exposure after statistical adjustments."

The Nunavik cohort participants were also evaluated at the age of 11 years with respect to various behavioral problems (Boucher et al. 2012b), total IQ (Jacobson et al. 2015), and measures of attention (Ethier et al. 2015). Exposure was measured in terms of PCB-153 concentration in cord blood and in the child's blood samples obtained at the time of testing. No associations were observed between WISC-based total IQ and PCB-153 levels in either cord blood or child's blood samples (Jacobson et al. 2015). The behavioral evaluation included a teachers' version of CBCL that provided scores for internalizing and externalizing problems and separately for attention problems, and the Disruptive Behavior Disorders (DBD) Rating Scale, which allows characterizing children with respect to signs of four conditions: ADHD-Inattentive type, ADHD Hyperactive-impulsive type, Oppositional Defiant Disorder, and Conduct Disorder (Boucher et al. 2012b). None of the associations between cord or child's blood PCB-153 levels and CBCL scores were statistically significant. The numeric results for Disruptive Behavior Disorders are not reported; however, the authors state that none of the exposures (other than lead and mercury) "significantly predicted any of the DBD-based diagnoses (data not shown)." A subsample (n=30) of 11-year-old study participants underwent an examination of attention using the Posner Attention-Shift Paradigm, which tests response to visual stimuli (Ethier et al. 2015). The dependent variables in all analyses included reaction time, errors of omission, false alarm

(i.e., errors of commission) accuracy and the validity effect. Of the 10 measures of association, one (errors of omission in relation to cord blood PCB-153) was statistically significant.

The second Nunavik cohort (Boucher et al. 2014) assessed PCB exposure based on cord blood levels and concentrations measured in breast milk samples collected at the postnatal interview. The first assessment of neurodevelopmental function took place when the children were 6.5 to 11 months of age and included FTII (both novelty and fixation subtests), BSID, (PDI and MDI) and A-not-B test. The A-not-B test is thought to assess working memory and includes two measures: length of delay, and percent of errors. The association with each of these measures was examined using cord blood PCB-153 as the exposure of interest and analyses were conducted for each age-specific assessment separately and together (using repeated measures models). One of the associations – between FTII novelty test and cord blood PCB-153 using the repeated measures model – was statistically significant. All other analyses for both cord blood and breast milk PCBs yielded null results, or were described in the text as not "predictive" without reporting quantitative results (Boucher et al. 2014).

In another study (Verner et al. 2010), the same cohort was re-examined using PCB-153 exposure at birth and postnatally; the former was measured in cord blood, and the latter was estimated using the pharmacokinetic model and expressed as PCB-153 blood levels at monthly intervals. The dependent variables of interest were the components the Behaviour Rating Scales (BRS) of BSID-II, and various measures ascertained from video recordings obtained during the administration of the BSID MDI. The results were mixed; for BRS the associations were not significant or opposite of the hypothesized direction, and for video recordings-based measures, some significant associations were observed for cord blood PCB-153, and some for estimated post-natal measures (Verner et al. 2010).

German cohorts (Dusseldorf and Duisburg)

The two German cohorts were established in the cities of Dusseldorf and Duisburg. Both cities are located on the river Rhine in the highly industrialized Ruhr area. The recruitment for the Dusseldorf cohort occurred from 1993 to 1995 and included 171 healthy mother-infant pairs identified at the obstetrical wards of three city hospitals (Walkowiak et al. 2001). The Duisburg cohort included 232 mothers recruited from 2000 through 2002 through a wide range of means such as informational leaflets posted at the area hospitals and clinical practices, media announcements, and personal contacts with individual health care providers (Wilhelm et al. 2008b).

The Dusseldorf cohort members underwent testing with BSID and FTII at the age of 7 months. (Walkowiak et al. 2001; Winneke et al. 1998). Using a two-sided type I error of <0.05 as the cutoff, none of the reported associations with PCBs measured as a sum of three congeners (138, 153 and 180) in cord blood and maternal milk were statistically significant.

The BSID test was administered again at the ages of 18 and 30 months, although the data for these analyses are limited to only 110 participants study (Walkowiak et al. 2001). The exposure categories were the same as at 7 months of age (sum of PCB-138, 153 and 180 in breast milk and cord blood) and the associations were examined for each age separately, and also across all age groups (7, 18 and 30 months) combined. One analysis – for PDI using data across all three ages

– demonstrated statistically significant inverse associations (based on a two-sided p-value <0.05). All other associations were not statistically significant or described in the text as "slightly positive."

By the age of 42 months only 87 children remained in the Dusseldorf cohort (Walkowiak et al. 2001; Winneke et al. 2005). These children were examined using the KAB-C test. The associations with cord blood and breastmilk PCBs were not statistically significant; for the association between KAB-C and PCBs measured in children's blood samples the two sided p-value was 0.05. When the children underwent KAB-C testing at the age of 6 years (Winneke et al. 2005) no significant associations were observed with any of the exposure metrics.

The two earliest publications based on the Duisburg cohort (Wilhelm et al. 2008a; Wilhelm et al. 2008b) presented results on the association between PCBs and NOS tests administered at 14 days of age, and again at the age of 18 months. In addition, mental and motor development was assessed using BSID at ages 12 and 24 months. Exposure was characterized as levels of individual congeners (118, 126, 138, 153, 165 and 180) in maternal blood and breast milk as well as various combinations of congeners and TEQ summary measures for various PCB categories (e.g., non-ortho, mono-ortho and total). No associations between any of the exposure metrics and neurological or developmental test results were observed.

When the children in the Duisburg cohort were 6-8 years of age (Winneke et al. 2014), they underwent an evaluation using the Pre-School Activity Inventory (PSAI), which relies on parental reports to assign a feminine and a masculine play behavior score. In the analyses of the masculine score in relation to maternal blood or breast milk PCBs (each expressed as a sum of dioxin-like TEQs), only the result for breast milk levels was significant, indicating lower masculine play in girls but higher (albeit non-significant) masculine play in boys (Winneke et al. 2014). Recall that these findings from the Duisburg cohort study were almost exactly the opposite to the corresponding findings from the Rotterdam study (Vreugdenhil et al. 2002b), which observed that masculine play was significantly lower in boys with higher PCB exposure, but the corresponding result was in the opposite direction and not significant in girls.

The Duisburg cohort members were further evaluated between ages 8 and 10 years using a wide range of behavioral measures. The results of these assessments are reported in two separate publications. The first publication (Neugebauer et al. 2015) included 15 different measures of attention administered using the Computerized Test Battery for Attentional Performance for Children, and the Parent Rating Scale for Attention-Deficit Hyperactivity Disorder, which provides four separate scores for inattention, hyperactivity, impulsivity and an overall ADHD score. The data on exposure in this publication included the sum of PCB 138, 153, 180 (μg/g lipid) and the sum of dioxin-like PCBs (expressed as TEQ). Each exposure metric was reported based on maternal blood and breast milk levels. In addition, lactational exposure to both PCBs 138, 153, 180 and dioxin-like TEQs was assessed by calculating their cumulative intakes. Of all the reported associations, five were statistically significant in the hypothesized direction and six were statistically significant in opposite to the hypothesized direction but without an identifiable pattern (Neugebauer et al. 2015).

The second publication administered the Social Responsiveness Scale (SRS), which relies on parental reporting to ascertain problems consistent with autistic behaviors, and a separate

parental questionnaire, which collects responses on 55 items to ascertain two measures – an Empathy Quotient and a Sympathy Quotient (Nowack et al. 2015). Exposure to PCBs was expressed as a sum of dioxin-like PCBs (TEQ) measured in maternal blood and in breast milk. The results were presented overall and separately for boys and girls. None of the associations among boys were statistically significant. Among girls, two associations were statistically significant, but in opposite to the hypothesized direction indicating less autistic behavior in participants with higher PCB exposure (Nowack et al. 2015).

INMA cohort

The INMA (INfancia y Medio Ambiente [Environment and Childhood]) cohort recruited pregnant women in several regions of Spain and followed their children from birth. Concentrations of various PCB congeners were measured in maternal and cord blood and in blood samples collected from children at the time of neurodevelopmental testing (Guxens et al. 2012).

Results for a subset of the INMA cohort participants (limited to one of the study sites) were reported in 2003 and expressed PCB exposure as a sum of congeners 28, 52, 101, 118, 138, 153, and 180 in cord blood (Ribas-Fito et al. 2003). The neurodevelopmental measures in that study were administered at the age of 13 months and included BSID (MDI and PDI) and the Griffiths Mental Development Scales, which are divided into five subscales (Locomotor, Personal-Social, Hearing and Language, Eye-Hand Coordination, and Performance). The results for BSID were significant only in the unadjusted analyses; however, after the associations were controlled for confounding factors, none of the associations were statistically significant. None of the results for Griffiths Scales were reported to be significant in the hypothesized direction.

The first evaluation of the full INMA cohort was reported when the children were "around 14 months" of age and included BSID testing as reported in two separate publications (Forns et al. 2012a; Gascon et al. 2013). In the first publication (Forns et al. 2012a), associations with BSID were examined for maternal blood levels of PCB-138, 153 and 180 and the sum of three congeners. The data for the sum of PCBs were also analyzed in a multipollutant model that controlled for co-exposures to other chemicals. The association with PDI was statistically significant for the sum of three PCBs in the single exposure model, but not in the multipollutant model. The associations with MDI were not statistically significant. In the second publication (Gascon et al. 2013), the INMA cohort data were re-examined using a pharmacokinetic model, which takes into account the absorption, distribution, metabolism and excretion of PCBs to estimate postnatal exposure at different ages. Only PCB-153 was considered in the model and none of the results were statistically significant. Unlike the earlier study (Forns et al. 2012a), the results for PDI and maternal blood PCB-153 in the second publication (Gascon et al. 2013) were statistically significant; however, the second analysis was based on a smaller sample (1175 vs. 1391).

When the INMA cohort was again examined at 4 years of age using MSCA the number of participants decreased to 405 (Forns et al. 2012c). Of those only 285 also provided blood samples at the time of testing. Notably, whereas the first publication (Forns et al. 2012a) used maternal blood samples to assess prenatal exposure and did not mention cord blood results, the second publication (Forns et al. 2012c) relied on cord blood results and did not mention maternal

blood levels. The associations with various MSCA components were observed in relation to cord blood PCB-153. In addition, there was a statistically significant association between cord blood PCB-138 and the Perceptual–Performance MSCA subset. All other analyses that focused on PCB-118, 138, 180 and the sum of all congeners, both in cord and child's blood samples produced null results.

In another analysis of the INMA cohort (Forns et al. 2012b) the neurodevelopmental measure of interest was the Continuous Performance Test administered at 11 years of age and the exposure was expressed as the sum of PCB-118, 138, 153 and 180 in cord blood and in samples obtained at the age of 4. Only one of the associations – reaction time in relation to PCB levels at 4 years of age – was statistically significant, but the authors reported that including other factors "in a multivariate regression, removed all statistical significance"

Faroe Islands cohorts

Two birth cohorts were established on the Faroe Islands approximately a decade apart. The first cohort was recruited at three hospitals in Torshavn, Klaksvik, and Suderoy from 1986 through 1987 with blood samples obtained from 1,023 infant-mother pairs (Grandjean et al. 1992). The second cohort included 182 children born at the Torshavn hospital during a 12-month period in 1994-1995 (Steuerwald et al. 2000).

The first cohort examined the associations of PCBs in cord blood, cord tissue, and child's blood with a wide range of neurodevelopmental measures among study participants at 7 years of age (Grandjean et al. 1997; Grandjean et al. 2001; Grandjean et al. 2012). These included the CPT (errors of omission and reaction time), Finger Tapping Test (preferred hand, other hand and both hands), Hand-Eye Coordination Test (error score), Bender Visual Motor Gestalt Test (copying errors and reproduction), certain components of WISC (Digit Span, Similarities and Block Design), Boston Naming Test (with and without cues) and California Verbal Learning Test (learning, short-term recall, long-term recall and recognition); a total of 17 different endpoints. In addition, the participants underwent an evaluation of visual and auditory function at 7 and 14 years of age (Grandjean et al. 2001; Murata et al. 2004).

In three publications (Grandjean et al. 1997; Grandjean et al. 2001; Murata et al. 2004) PCBs (sum of 138, 153 and 180 congeners multiplied by 2) were measured as wet weight- and lipid-adjusted cord tissue levels. The first study was based on the data from 917 participants who underwent testing using a battery of neurodevelopmental tests. The results for PCBs, after adjusting for mercury exposure, are presented for only four measures (CPT reaction time, Boston Naming Test with and without cues and California Verbal Learning Test long-term recall). Only p-values were reported; all were greater than 0.05 (Grandjean et al. 1997).

In the second study (Grandjean et al. 2001), the numbers of participants across the analyses ranged from 288 to 425. The results were statistically significant for 2 out of 17 measures (average reaction time on Continuous Performance Test and Boston Naming Test without cues) when exposures were based on wet-weight samples and for none of the lipid-adjusted levels. In addition, 379 and 382 children in that study underwent evaluation of visual and auditory evoked potential latencies, respectively; 295 children were also tested for auditory thresholds; and 393 children had the Functional Acuity Contrast Test. These auditory and visual tests collectively

included 36 different endpoints examined across 82 different analyses (with or without adjustment for lipids or mercury levels). Five of those 82 measures of association were statistically significant without any evidence of a pattern.

Auditory function was evaluated again when the participants were 14 years of age (Murata et al. 2004). The data were based on 878 eligible children. The numeric results are not presented; however the authors state that "the PCB parameter did not reach statistical significance in any of the analyses."

In a more recent article (Grandjean et al. 2012) the results for the same neurobehavioral tests were reported for a larger group of participants (N=923). The CPT, Finger Tapping Test, Hand-Eye Coordination Test and Bender Visual Motor Gestalt Test were examined separately and in combination (termed "motor outcomes"). Similarly, Digit Span, Similarities and Block Design components of WISC, Boston Naming Test and California Verbal Learning Test were examined individually and as a combined "verbal outcomes" measure. Instead of cord tissue, PCBs were measured in cord blood. Some of the observed results were statistically significant. These included associations of PCB-118 with the CPT errors of omission and Boston Naming Test with cues, association between PCB-138 and WISC Block Design, and association between PCB-153 and Boston Naming Test with cues. Notably not all results were adjusted for mercury exposure, but when they were, the associations were no longer statistically significant.

The second Faroese cohort was evaluated only once, at around 2 weeks of age (Steuerwald et al. 2000). The PCB exposure was measured as a sum of 28 non-specified congeners in maternal blood and breast milk obtained 4-5 days postpartum. The tests of interest included NOS, overall and separately for muscle tone and reflexes. There were no associations between various PCB measures and NOS scores.

Japanese cohorts (Hokkaido and Tohoku)

The investigators of the Hokkaido cohort recruited pregnant women between July 2002 and October 2005 from a large hospital in the city of Sapporo (Nakajima et al. 2006; Nakajima et al. 2017). Most women provided 40-mL blood sample "after the second trimester" although for some women the samples were obtained after delivery. The samples were analyzed for 14 different congeners categorized as non-ortho (77, 81, 126, and 169), mono-ortho (105, 114, 118, 123, 156, 157, 167, and 189) and di-ortho (170 and 180) PCBs. Associations with BSID MDI and PDI scores were examined for each congener separately (except PCB-81, which was not detected) and for three different combinations (non-ortho, mono-ortho and total coplanar) each expressed in two ways: as pg/g lipid and as TEQs.

The first publication evaluated 134 children at the age of 6 months and reported no statistically significant associations with either MDI or PDI (Nakajima et al. 2006). In a more recent study (Nakajima et al. 2017), the number of 6-month-old participants increased to 190 due to extended recruitment and the results were reported separately for boys and girls. Among all reported associations, several results for PDI were statistically significant in boys but not girls, and one was significant in girls but not boys. When 121 of 190 children were retested at the age of 18 months (Nakajima et al. 2017), none of the results for PDI were statistically significant. For

MDI, several analyses demonstrated that higher PCBs exposure was associated with better test performance, but these results were only observed in girls and not boys.

At the age of 3.5 years 141 remaining cohort participants underwent the KAB-C test (Ikeno et al. 2018). The results of testing were summarized as an overall mental processing summary scale and an achievement scale. All associations were presented both overall and separately for boys and girls, each expressed as two measures: a correlation and a regression coefficient. Only one of these multiple associations (between the sum of non-ortho PCBs and the overall mental processing summary scale among boys) was statistically significant and inverse. Several associations, especially for achievement scale among girls, were statistically significant, but in the opposite direction, indicating better scores among participants with higher PCB exposures.

The Tohoku cohort was assembled between 2001 and 2003 in northern Honshu, the largest island of the Japanese archipelago. Maternal and cord blood samples were collected at 28 weeks of pregnancy and at delivery, respectively; in addition, mothers were asked to provide a sample of breast milk one month after giving birth (Nakai et al. 2004).

The first evaluation of the Tohoku cohort took place at 3 days of age and involved NBAS testing (Suzuki et al. 2010). The exposure variable was the sum of all 209 PCB congeners in cord blood. The crude (unadjusted) analyses demonstrated statistically significant associations for three NBAS clusters: orientation, regulation of state, and motor; however for the first two of these clusters the associations were in the opposite of the hypothesized direction. When the data for motor cluster were examined in a series of multivariable analyses the previously observed association with PCBs was no longer statistically significant, and even changed direction in the fully adjusted model (Suzuki et al. 2010).

When the children were 2 to 3 years of age they underwent another evaluation using the Child Behavior Checklist (Tatsuta et al. 2012). PCB exposure in that study was also expressed as a sum of all measured congeners on cord blood. In the unadjusted analyses, sum of cord blood PCBs was significantly correlated with internalizing, but not with externalizing or total scores. The association with the internalizing score was no longer evident once the results were controlled for confounders (Tatsuta et al. 2012).

At the age of 3.5 years the children were tested again using the Japanese version of KAB-C (Tatsuta et al. 2014). Unlike previous publications (Suzuki et al. 2010; Tatsuta et al. 2012), exposure in that article was expressed in terms of PCB homologs: monochlorobiphenyl (1 CB), dichlorobiphenyl (2CB), trichlorobiphenyl (3 CB), etc. Only the association with one of the ten homolog groups (9CB) was statistically significant for two of the four KAB-C scales - sequential processing score and the overall cognitive (termed “mental processing”) scale. Moreover, the association between 9 CB and mental processing was only evident in boys and not in girls. No associations were observed for the sum of all PCBs (Tatsuta et al. 2014).

New Bedford, MA cohort

This cohort included 788 mother–infant pairs who resided near a harbor in New Bedford, Massachusetts. Of those, 539 (68%) underwent NBAS assessment at birth, 542 (69%) were tested at 2 weeks of age, and 408 (52%) had both exams (Sagiv et al. 2008). The cord blood

samples were analyzed for 51 PCB congeners, but exposure was characterized using two measures: the sum of four prevalent PCB congeners (118, 138, 153, and 180) and computed TEQ for the sum of the five dioxin-like mono-ortho PCB congeners. Unlike other studies using NBAS test, the New Bedford cohort investigators defined the dependent variables of interest based on subscales or newly created endpoints such as "consolability" or "never in state to do orientation items." With respect to traditional NBAS clusters, the only results available are for orientation, habituation, and regulation of state; none were reported to be related to the exposures of interest. For other measures, the authors reported significant associations with "quality of alertness" (both exposures), "cost of attention" (mono-ortho PCBs only), and "consolability" (mono-ortho PCBs only). No significant associations with either exposure were observed for "alertness", "self-quieting", hand-to-mouth", irritability", "never in state to do orientation items", "elicited activity", "spontaneous activity" and "motor maturity" When the data were examined across two assessments, defined as "failure to recover" the authors reported "no consistent patterns".

The New Bedford cohort participants were examined again around 8 years of age with results reported in three publications (Sagiv et al. 2010; Sagiv et al. 2012; Verner et al. 2015). Two of those studies (Sagiv et al. 2010; Verner et al. 2015) evaluated study participants based on the 59-item Conners' Rating Scale questionnaire administered to teachers. The scale includes four measures of behaviors associated with attention deficit hyperactivity disorder (ADHD): 1) Conners' ADHD Index, 2) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Inattentive 3) DSM-IV Hyperactive-Impulsive, and 4) DSM-IV Total (both subtypes combined). The number of participants ranged from 487 to 573 depending on the statistical analysis used. Cord blood samples were analyzed for 51 individual PCB congeners. In the first study (Sagiv et al. 2010), PCB exposure was measured as the sum of all 51 congeners, the sum of 4 most prevalent congeners (118, 138, 153, and 180); and the computed TEQ for the sum of the dioxin-like mono-ortho PCBs 105, 118, 156, 167, and 189). The data were analyzed based on two approaches; a linear regression, which used PCB levels and log-transformed Conner's scores as continuous variables and a log risk model, which calculated relative proportions of children who scored above the 86th percentile across exposure quartiles. Significant associations were observed with two of the Conners' measures - ADHD Index and DSM-IV Total, but the results were mixed for the Inattentive and Hyperactive-Impulsive scales (Sagiv et al. 2010).

The same data were re-examined a few years later using alternative exposure assessment methodology (Verner et al. 2015). Congener 153 was used as a proxy for total PCBs exposure at birth and postnatally; the former was measured in cord blood, and the latter was estimated using the pharmacokinetic model and expressed as PCB-153 concentrations in child's blood at monthly intervals. Unlike the earlier study (Sagiv et al. 2010), the re-analysis used quantile regression based on the 50th and the 75th percentiles of the Conners' scales as the alternative cutoffs. The results were mixed and cutoff-dependent. Using the 75th percentile quantile regression, the associations with cord blood and early postnatal levels were significant for three out of four Conners' measures. By contrast a 50th percentile quantile regression demonstrated no discernible associations (Verner et al. 2015).

The third study of school-age children enrolled in the New Bedford cohort (Sagiv et al. 2012) included two components of WISC (Processing Speed and Freedom from Distractibility) and

four measures derived from the Continuous Performance Test (errors of omission, errors of commission, reaction time and reaction time variability). The data were presented separately among boys and girls for the sum of PCB-118, 138, 153 and 180 and for the total TEQ of mono ortho congeners in cord blood. The results for WISC Processing Speed were mixed with inverse associations observed for boys, but not for girls and not for all children examined together. The results for WISC Freedom from Distractibility were not statistically significant regardless of exposure measure across all groups of participants. Reaction time on the Continuous Performance Test was shorter (i.e., better) in relation to higher PCB exposures among girls, but there was no association among boys. The errors of omission rate was increased in relation to one of the exposures (mono ortho PCBs), but only among boys. No associations were observed for errors of commission.

In another recent study (Orenstein et al. 2014), 393 members of the New Bedford cohort were assessed at 8 years of age using the Wide Range Assessment of Memory and Learning (WRAML) test. The dependent variables in these analyses included three WRAML indices – Visual Memory, Verbal Memory, and Learning. Each of these indices was evaluated in relation to two PCB measures - the sum of congeners 118, 138, 153 and 180 and the weighted TEQ sum of dioxin-like PCBs (105, 118, 156, 167, and 189). None of the 6 associations was statistically significant (Orenstein et al. 2014).

Eastern Slovakia cohort

Members of this cohort were women recruited at the time of delivery at two hospitals in eastern Slovakia between 2002 and 2004. Two publications (Park et al. 2009; Park et al. 2010) were based on the cohort of children born to study participants and evaluated using BSID around 16 months of age. Maternal and cord blood samples were available for 1076 and 469 children, respectively; however exposure was assessed on a small subset of participants. The first study (Park et al. 2009) measured exposure based on levels of hydroxylated PCBs (OH-PCBs) in 202 maternal and 92 cord blood samples. The association with BSID was significant for just one hydroxylated congener (4-OH-PCB-107), but not for OH-PCB-153, -146, -138, -187 or -172 and not for the combination of all six OH-PCBs. The second study (Park et al. 2010) measured several non-hydroxylated PCB congeners in cord and maternal blood. The analyses demonstrated statistically significant associations for both PDI and MDI with PCB-118, PCB-156 and the combination of these two congeners. There was also a statistically significant association between cord blood (but not maternal blood) PCB-138 and PDI. None of the associations for PCB-153, PCB-170 and PCB-180 and for combinations of most common or "anti-estrogenic" congeners were statistically significant.

Four more recent papers focused on the hearing function among the Slovakia cohort participants (Jusko et al. 2014; Kostiakova et al. 2016; Palkovicova Murinova et al. 2016; Sisto et al. 2015). All four studies used Distortion Product Otoacoustic Emissions (DPOAE) testing as a measure of hearing function, where OAEs are sounds of cochlear origin, which can be recorded in the ear canal. The participants underwent DPOAE testing at 45 and 72 months of age. The methods sections indicate that all three studies had data on 15 congeners; however, only PCB-153 was used in the analyses.

In the first of the three publications (Jusko et al. 2014) exposure was expressed as PCB-153 levels in maternal and cord blood samples as well as in several blood samples drawn from the children at 6, 16 and 45 months of age. In addition, the authors created a composite measure termed "postnatal average". Although DPOAE is performed using a range of frequencies and separately to each ear, the dependent variable in the analyses was the average DPOAE. The results for maternal and cord blood PCB-153 were not significant. The blood levels at 6 months of age were related to average DPOAE only in the crude but not in the adjusted models. Both of the remaining blood measures (at 16 and 45 months) were significantly associated with average DPOAE, as was the postnatal average PCB-153 exposure (Jusko et al. 2014)

The second paper assessing DPOAE at 45 months of age (Sisto et al. 2015) reported the results for each of the 11 frequencies (range; 1000-5657 Hz) averaged across both ears. Unlike the earlier paper (Jusko et al. 2014) the results for maternal blood and postnatal average were no longer reported. All associations with cord blood PCB-153 were in the opposite of the hypothesized direction with four of 11 frequency-specific results statistically significant. The corresponding results for child's blood levels were all in the hypothesized direction, with five of 11 frequency-specific results consistently statistically significant across samples drawn at different times (Sisto et al. 2015).

The third publication from the Slovakia cohort evaluated DPOAE measures at 6 years of age in relation to PCB-153 levels in blood samples drawn at 45 months and at the time of testing (Palkovicova Murinova et al. 2016). In addition to 11 frequency-specific DPOAEs the study also evaluated two additional measures – DPOAE growth and pure tone audiometry. The DPOAE growth included 7 different measures reflecting DPOAE responses at a constant frequency as a function of the stimulus level. Pure tone audiometry assessed hearing level, expressed in dB, and evaluated at 125, 250, 500 Hz, 1000, 2000, 4000, and 8000 Hz. Two of the 11 DPOAE results were significantly decreased in relation to higher PCB-153 levels at both ages. The remaining measures were not shown to be consistently associated with PCBs (Palkovicova Murinova et al. 2016).

In another recent article addressing the same issue (Kostiakova et al. 2016) DPOAE measures were examined in relation to "integrative exposure assessment in time" that estimated an area under the curve for PCB-153 in child's blood at different ages. The reported results focused on findings at 45 months of age and primarily on results for right ears among boys where some associations were found to be statistically significant. The authors reported that for girls they "did not observe any significant relationships between DPOAEs amplitudes and PCB serum concentration (data not shown), nevertheless the directional trend was similar." The authors also state that at 72 months of age "DPOAE amplitudes were not systematically related to perinatal exposures either in boys or girls in a similar way as with 45 months data." (Kostiakova et al. 2016)

The most recent publication based on the Eastern Slovakia cohort administered Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) at 6 years of age (Drobna et al. 2019). The specific test components used in the analyses included eight measures: Block design, Information, Matrix reasoning, Vocabulary, Picture concept, Symbol search, Word reasoning, and Coding as well as the Composite score. Each of these measures was examined in relation to levels of PCB-118 and PCB-153 in blood samples of children obtained at the time of testing.

The authors reported "PCB-153 and PCB-118 were not statistically significantly associated with WPPSI-III in any of investigated models." (Drobna et al. 2019)

HOME cohort

The Health Outcomes and Measures of the Environment (HOME) Study is a birth cohort that recruited 468 pregnant women who received care at one of the clinics in and around the city of Cincinnati, Ohio (Braun et al. 2017). Women provided urine and blood samples at 16 and 26 weeks of pregnancy. The blood samples were analyzed for multiple chemicals including PCBs. Children of participating women were assessed with respect to their neurological and behavioural function within 48 hours after birth. Between 1 and 8 years of age the same children also underwent testing using BSID-II, WPPSI-III and WISC-IV and several instruments evaluating language abilities, reading skills, academic achievement and play behaviors (Braun et al. 2017).

By the age of 4 and 5 years 222 children completed at least one follow-up visit. Of those, 175 children were included in the analyses evaluating the association between maternal blood levels of PCBs and Social Responsiveness Scale (SRS), which relies on maternal reports to ascertain problems consistent with autistic behaviors (Braun et al. 2014). The authors reported collecting data on 36 PCB congeners; however, for some congeners the frequency of detection was less than 20%. For this reason, analyses of the association with SRS were based on maternal blood levels of 25 congeners or congener combinations. Each association was examined using 10 alternative statistical models. Only one association, with PCB 138/158, was statistically significant in 2 of the 10 models. On the other hand, several associations (e.g., with PCB 178 in three multipollutant models) were significant in the opposite direction.

In a more recent analysis of the HOME cohort data, 203 children underwent evaluation of reading skills using Woodcock-Johnson Tests of Achievement-III (WJ-III) at the age of 5 years and Wide Range Achievement Test 4 (WRAT-4) at the age of 8 years (Zhang et al. 2017). The results of WJ-III were expressed as Basic Reading and Brief Reading scores and the results of WRAT-4 were expressed as the Composite Reading score. The association with PCBs was only presented for one exposure – the sum of PCB-118, -153, -138/158, and -180 in maternal blood. No significant associations were observed. In the same publication the authors also present the results for the sum of the same four PCB congeners in relation to two additional dependent variables – full IQ based on WISC and the Behavioral Assessment System for Children-2 (BASC-2) – both administered at 8 years of age. Once again no significant associations were observed (Zhang et al. 2017).

Another recent study of 214 children enrolled in the HOME cohort evaluated the association between the sum of not specified PCBs (15 congeners) measured in maternal blood and Continuous Performance Test at 8 years of age (Vuong et al. 2017). The dependent variables in that study included several Continuous Performance Test-derived indices, including errors of omission, errors of commission, reaction time and tau (τ), the exponential component of the reaction time distribution. The results for PCBs were only presented for two of those indices – errors of omission and tau; both demonstrated no association (Vuong et al. 2017).

Summary

A review of the within-cohort data indicates that none of the studies observed a consistent and sustained association between one or more PCB exposures and neurodevelopmental measures. In addition, it is clear that most cohort studies included in this review presented only a fraction of the available results. Although there may be circumstances when reporting each association is not necessary, it is also clear that the literature on PCBs and neurodevelopment is greatly affected by selective reporting. The preceding sections of this report offer multiple examples of selective such reporting. **Table 1** (p. 86) illustrates this issue further by showing that most cohort studies reported less than 50% of possible associations for which they clearly had exposure and neurodevelopmental test information. It is likely that the actual number of possible associations is even higher because some publications mentioned collecting data on certain exposures and neurodevelopmental measures without ever using these data in any of the analyses. For example, the Faroe Islands cohort (Steuerwald et al. 2000) performed laboratory analyses of both maternal and cord blood samples, but only reported the former. Similarly, the Oswego cohort administered the Continuous Performance Test, which usually is expressed in terms of reaction time, total number of correct or erroneous responses and errors of commission and omission, but reported results only for errors of commission and total correct responses (Stewart et al. 2005).

These data indicate that on average the proportion of statistically significant results among all possible associations across the cohorts was well within 5%. This is consistent with an expectation that in the presence of multiple hypotheses testing statistically significant findings attributable to chance alone should account for roughly one out of 20 possible results.

Some of the postnatal PCB measures may have been obtained later in life and could not precede the tests administered at younger ages. Therefore to assure temporality, in a separate analysis, I restricted exposures to those measured prenatally or within the first month of life. As shown in **Table 2** (p. 87), this restriction did not change the results.

DO POPULATIONS WITH HIGHER PCB EXPOSURES EXPERIENCE MORE ADVERSE NEURODEVELOPMENTAL EFFECTS?

One possible explanation of the inconsistency across studies reviewed in the previous sections of this report is the difference in the levels of exposure. Thus, it is expected that a truly causal association would emerge more readily in populations with higher PCB exposures. This is not necessarily the same as 'dose-response' because the concept of dose-response implies that a specific association is addressed consistently across studies. Nevertheless, even if the studies are dissimilar, one would expect that research conducted in populations with higher exposure levels would tend to observe stronger results.

It is also important to point out that a direct comparison of PCB levels across cohorts based on published data is difficult because the results of exposure assessments may differ greatly depending on the congeners examined, laboratory protocols, lipid-adjustment, limits of detection, and types and volume of samples (Brouwer et al. 1999).

To overcome this difficulty Longnecker and colleagues contacted investigators of several cohort studies and requested available data and samples from each cohort. The goal was to express the exposure levels from all cohorts in a consistent fashion based on the original data, and if necessary, laboratory re-analyses of samples to achieve maximum standardization. The main results were expressed as the median level of PCB 153 concentrations in prenatal maternal serum (Longnecker et al. 2003).

Table 3 (p. 88) summarizes results of these analyses by presenting median PCB-153 concentrations for each cohort in descending order (range: 30-450 ng/g lipid). In addition, the study reported a ratio of median PCB-118 to median PCB-153 for each cohort, and thus it is also possible to characterize the same studies with respect to median PCB-118.

Although rankings based on PCB-153 and PCB-118 levels are not identical, the top two studies (Faroe Islands and CPP) are the same for both congeners. Moreover, studies ranked 3rd and 4th for PCB-153 (Dusseldorf and California) are also ranked relatively high with respect to PCB-118. An evaluation of findings from these four studies allows assessing evidence of dose response at least with respect to prenatal exposures, as captured in the Longnecker et al. (2003) publication.

The PCB data for the highest-ranked cohort included in the Longnecker et al. paper came from the smaller Faroese study, which was evaluated only once, at around 2 weeks of age (Steuerwald et al. 2000). As discussed in the previous sections, the neurodevelopmental tests of interest in that study included NOS, overall and separately for muscle tone and reflexes. There were no associations between various PCB measures and NOS scores in any of the analyses. The data on the larger Faroese cohort (Grandjean et al. 2001; Grandjean et al. 2012) are not included in the Longnecker et al. (2003) analysis; however it is reasonable to assume that the exposures in the two cohorts were comparable. The two studies by Grandjean et al. evaluated 10 different exposures and 58 different neurodevelopmental measures; with less than 5% of the possible associations found to be statistically significant (i.e., well within of what is expected due to chance alone). Notably, the few observed associations were no longer evident once the results were lipid-adjusted or controlled for mercury exposures.

The second-ranked CPP cohort was perhaps the strongest study from the methodological point of view. A distinguishing feature of this study is that all participants underwent testing at different ages without any knowledge of their exposure status because analyses of PCBs were conducted on archived prenatal samples after the data on neurodevelopmental measures were already collected. Notably none of the CPP analyses demonstrated evidence that prenatal PCB exposure was related to adverse test results.

The CPP cohort data offer an additional opportunity to assess whether associations between PCBs and neurodevelopmental measures are more likely found in populations with higher exposure levels. In one the CPP publications (Daniels et al. 2003) the data are presented for each of the 12 study sites. As shown in Table 3 of that publication (p. 490) median PCB exposures (all congeners) ranged from 1.6 in Portland, OR to 3.7 µg/L in Richmond, VA. One would expect that, if PCBs had a truly harmful effect on neurodevelopment, a site such as Richmond would demonstrate the strongest inverse association with the results of neurodevelopmental tests (in this case BSID). An inspection of the data contradicts this expectation. While the regression slope in Portland was negative but not statistically significant (-1.6, p=0.31 for MDI and -1.7, p=0.46 for PDI), the association in Richmond was in the opposite direction, and in the analyses for PDI statistically significant (3.5, p=0.03).

The study from Dusseldorf ranked third for PCB-153 and sixth for PCB-118. The Dusseldorf cohort observed a few mixed results (based on two-sided tests, most were not significant); however, these results were in relation to breast milk, rather than prenatal cord blood exposure. When discussing BSID results Walkoviak et al. (2001) state the following (p. 1604): "All associations with cord blood PCB and the Bayley Scales of Infant Development mental score were small and even slightly positive. Association between the Bayley Scales of Infant Development motor score and PCB was negative and very small." When discussing results for KAB-C the same authors state: "The associations between cord blood PCB and the Mental Processing Composite-Index of the Kaufman Assessment Battery for Children at 42 months were small and even slightly positive." (p. 1605)

The results on the association between PCB and neurodevelopmental measures are not readily available for the California Child Health and Development Studies cohort, which ranks fourth with respect to PCB-153 and third with respect to PCB-118 levels. The data pertaining to this cohort were included in the Longnecker et al. (2003) publication and the study was reported to collect and analyze maternal blood samples for PCBs (James et al. 2002). A search of peer reviewed literature did not reveal any relevant publications from this cohort although the study website (http://www.chdstudies.org/research/publications.php) lists 234 peer reviewed articles addressing a wide range of other research questions. The only evidence that the relevant data were indeed analyzed comes from a list of conference presentations on the same website, which includes Yu et al. “Prenatal Organochlorine Exposure, Maternal Thyroid Function and Neurocognitive Development”, presented in 2011 at the Society for Epidemiologic Research North American Congress in Montreal. A search of proceedings from that conference identified one abstract (#044-S) with the same first author, but slightly different title “Prenatal Organochlorine Exposure, Maternal Thyroid Function and Neuromotor Development.” In the abstract, the authors reported evaluating an association between various organochlorine compounds in maternal blood and neurodevelopmental measures at 5 years of age. The tests

included the Lincoln-Oseretsky Motor Development Scale (MDS), the Goodenough-Harris Draw-A-Man Test (DMT), and the Gesell Figures (GF) test. The authors reported: "No associations were found between OCs and MDS in boys. We also found a small association between PCB203 and MDS in girls. No associations were found between any OC and DMT or GF…"

Taken together these data indicate that none of the cohorts with relatively high prenatal PCB exposures as measured by maternal blood levels of PCB-153 and PCB-118 demonstrated detectable adverse effects of these exposures. In addition, an examination of the data from the multi-site CPP cohort indicates no evidence that children in locations with higher PCB levels were more likely to experience neurodevelopmental problems.

DO PCB-EXPOSED CHILDREN IN THE GENERAL POPULATION EXPERIENCE GREATER INCIDENCE OF NEURODEVELOPMENT-RELATED DIAGNOSES?

As I explained in the section "Statistical and clinical significance of associations", if the association with a particular neurodevelopmental measure is real, one would also expect a greater likelihood that children with higher levels of exposure are more likely to receive a clinical diagnosis of a related condition. The current literature includes studies that focused on two specific clinical diagnoses; autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD). While there are many studies that relied on neurodevelopmental and behavioral testing, the publications on ASD and ADHD diagnoses are relatively sparse. Those studies are discussed below.

PCBs and Autism Spectrum Disorder

Among all studies that met the criteria for inclusion in this report, only one, the Finnish Maternity Cohort, focused on clinical ASD diagnoses. The Finnish Maternity Cohort includes data on more than 1 million pregnancies with archived prenatal serum specimens drawn since 1983 from more than 98% of eligible women. In Finland, a diagnosis of ASD is based on an extensive multidisciplinary assessment and most ASD cases are treated free of charge and are documented in the Outpatient and Hospital Discharge Register (Lampi et al. 2011). The ability of the Finnish Maternity Cohort to ascertain virtually all new ASD diagnoses serves as the premise for the Finnish Prenatal Study of Autism. Two publications used the data from this study to examine the association between PCB exposure (as measured in maternal blood samples) and autism diagnosis (Brown et al. 2018; Cheslack-Postava et al. 2013).

The earlier of the two publications (Cheslack-Postava et al. 2013) reported the results of a pilot study that compared 75 ASD cases and 75 controls selected among children born from 1991 to 2000 who had maternal blood samples available. Exposure to PCBs was expressed as concentrations of individual PCB congeners 118, 138, 153, 156, 170 and 180, as well the sum of all congeners and three composite measures: TEQ for dioxin-like PCBs, neurotoxic equivalent (NEQ), and a thyroid-hormone based TEQ. The authors noted that they observed no case-control differences in PCB distributions "near the middle of the exposure range, but possible differences at the high end of the range." For this reason they defined exposure as a binary variable using the 90^{th} percentile as the cutoff. The data analyses produced no statistically significant results, but the authors noted a few non-significant associations that warranted follow up in a full scale study.

The full scale analysis of the Finnish Prenatal Study was published 5 years later (Brown et al. 2018). In this publication, the authors compared 778 ASD cases to 778 controls selected from the same birth cohort and conducted analyses that were similar to those reported in the pilot study with two differences: the cutoff for high exposure was drawn at the 75^{th} rather than 90^{th} percentile, and unlike the first study the results were adjusted for maternal age, parity and psychiatric disorders. The results of the expanded analyses demonstrated no evidence of an association between PCBs (taken individually or as a sum) and ASD (Brown et al. 2018).

Another study that evaluated the association of PCBs with ASD or related conditions was based on the Markers of Autism Risk in Babies – Learning Early Signs (MARBLES) study. The

MARBLES birth cohort includes children whose older siblings were diagnosed with ASD (Granillo et al. 2019). Maternal blood samples were collected during prenatal visits and analyzed for PCB-11, 28, 52, 66, 77, 84, 91, 95, 101, 118, 131, 132, 135, 136, 138, 149, 153, 174, 175, 176, 180, and 196. Unlike the Finnish birth cohort study (Brown et al. 2018), cases of ASD in the MARBLES cohort were not defined based on clinical diagnoses, but rather from two research instruments, Autism Diagnostic Observation Schedule (ADOS) and Mullen Scales of Early Learning (MSEL). Two types of conditions were ascertained – ASD, and non-typical development (non-TD). The Non-TD category included children who did not meet the criteria for ASD, but had low MSEL or high ADOS scores. Analyses focused on the associations with both ASD and non-TD for each congener individually as well as three combinations of PCBs – all measured congeners, Dioxin-Like PCBs (77 and 118) and the sum of PCB-52, 84, 95, 136, and 176, which are thought to be interacting with the ryanodine receptor (RyR). In the analyses for individual congeners significant association with ASD in the hypothesized direction was observed for PCB-101, however two other congeners PCB-175 and PCB-176 were associated with lower odds of ASD. None of the individual congeners were associated with non-TD. No statistically significant associations were observed with any of the summary measures (Granillo et al. 2019).

A review of the literature on ASD and PCB would be incomplete without discussing the Markers for Autism (EMA) study from California. Although EMA is not a birth cohort study, it is often mentioned in the literature, and for this reason warrants a discussion. To-date the results on the association between PCB and ASD were reported in two EMA publications (Lyall et al. 2017; Hamra et al. 2019). The first publication compared 545 cases of ASD and 181 cases of intellectual disability (ID) without autism to 418 general population controls (i.e., children without ASD or ID) with respect to maternal blood levels of PCB-28, 99, 118, 138/158, 153, 170, 180, 187, 194, 196/203, 199 and a sum of all measured congeners (Lyall et al. 2017). Two of these exposure measures (PCB-138/158 and PCB-153) were significantly associated with ASD, and PCB-138/158 was also associated with ID when the PCB levels were divided into quartiles. It is important to point out however, that when the same analyses were conducted by comparing the top and the bottom 10^{th} percentiles of the PCB distributions, the associations of both PCB-138/158 and PCB-153 with ASD weakened instead of strengthening (Lyall et al. 2017). It is also important to note that the previously cited Finnish study (Brown et al. 2018) specifically focused on PCB-138 and PCB-153 with the goal of replicating the Lyall et al (2017) results. The Finnish authors reported no associations for either PCB 138 or PCB 153 (Brown et al. 2018).

More recently, the same EMA data were re-examined by using the more advanced Bayesian approaches and by taking into consideration other chemicals, not just PCBs (Hamra et al. 2019). Bayesian methods are designed to combine what is expected (or known) about effects of various exposures with what can be estimated from a given dataset. Although Bayesian analyses are dependent on certain assumptions, they allow overcoming the problems of multiple comparisons, which often present a challenge in studies that collected data on a wide range of chemicals such as PCBs. When this approach was applied to the EMA data, there was no evidence that any of the PCBs, including 138/158 and 153 congeners were related to either ASD or ID (Hamra et al. 2019).

PCBs and Attention Deficit Hyperactivity Disorder

The association between PCBs and ADHD diagnosis was examined in two Scandinavian birth cohort studies (Lenters et al. 2019; Strom et al. 2014). Both studies, one in Denmark and the other in Norway, were able to take advantage of existing nationwide registry data in their respective countries.

The Danish publication (Strom et al. 2014) obtained the data from the Danish Fetal Origins 1988 (DaFO88) study, which recruited pregnant women in the city of Aarhus in the period 1988–89. Among 1212 eligible women 965 (80%) were enrolled and provided blood samples for future analyses. PCB exposure was assessed as a sum of congeners 118, 138, 153, 156, 170, and 180 in maternal serum. Information on diagnoses of interest was obtained by linkage to population based registries that contain information in new diagnoses and prescription medications. An ADHD case was defined based on the evidence of at least one prescription for psychostimulant medication or registered a documented diagnosis of "hyperkinetic" disorder. No significant associations between PCBs and ADHD were observed. Additional analyses focusing on incidence of depression and academic achievement in school also yielded no significant results (Strom et al. 2014).

The study in Norway (Lenters et al. 2019) used data from the Human Milk Study (HUMIS) prospective birth cohort, which recruited new mothers and their babies around 2 weeks after birth in seven counties. Breast milk samples were analyzed for PCB congeners 74, 99, 105, 114, 118, 138, 153, 156, 157, 167, 170, 180, 189 and 194. ADHD cases were identified by linkage to the Norwegian Patient Registry, which includes all confirmed diagnoses from hospitals or outpatient clinics. The analysis examined the associations of each of 14 PCB congeners with ADHD using a variety of alternative statistical models. None of the results were statistically significant in the hypothesized direction, although in some of the models (e.g., for PCB-118, PCB-153 and sum of all congeners) higher exposure was associated with significantly lower odds of ADHD (Lenters et al. 2019).

The largest study conducted to-date examined the association of prenatal and postnatal PCB-153 exposure with ADHD using pooled data from seven European cohorts (Forns et al. 2018). Only one of those cohorts (the previously mentioned Norwegian HUMIS study) used clinical diagnoses to ascertain ADHD. In all other cohorts ADHD was defined based on a variety of checklists and questionnaires. The authors chose PCB-153 as a congener of interest with cord blood levels used as a measure of prenatal exposure and postnatal exposure at 3, 6, 12 and 24 months of age estimated using pharmacokinetic model. The results of the pooled analyses demonstrated no evidence that PCB-153 at birth or at any of the postnatal intervals was associated with ADHD (Forns et al. 2018)

Summary

Taken together these data indicate that claims about the potential associations of PCB exposure to both ASD and ADHD are not supported by scientific evidence. In two instances, earlier suggestive findings on ASD (Cheslack-Postava et al. 2013; Lyall et al. 2017) were not confirmed in more definitive follow up analyses by the same groups of authors (Brown et al. 2018; Hamra

et al. 2019). The data on ADHD also provide no evidence that PCB exposures either prenatally or later in life affect the likelihood of being diagnosed with this condition.

Another informative, albeit indirect, line of evidence to support the above conclusions comes from the data on long-term population trends. If PCBs were an important contributor to ASD or ADHD, the changes in incidence for both of these conditions would be expected to follow the changes in PCB levels over time. In fact, the opposite is true. While both prenatal and postnatal exposures to PCBs have been declining for years (Fang et al. 2015; Ma et al. 2014; Sjodin et al. 2004), prevalence estimates for both ASD and ADHD diagnoses appear to be increasing (Nevison et al. 2018; Xu et al. 2018).

A REVIEW OF THE EXPERT REPORT BY JAMES OLSON, PHD

In preparation of this report I was also asked to review the expert opinion provided by Dr. James Olson. Dr. Olson claims to have reviewed the literature that allows him to draw a conclusion that "PCBs cause an increased risk" of "neurobehavioral effects "in the general population at background, environmental levels of exposure"

To support his opinion Dr. Olson cites a very limited number of original studies. It is very important to keep in mind that the literature on PCBs is voluminous, variable in quality and extremely heterogeneous. It takes a serious effort to understand and process this amount of information in a systematic fashion. Unfortunately, the extraordinary number of readily accessible and often conflicting publications also opens opportunities for biased and selective reviews. Dr. Olson's expert report is an example of such biased and selective review. The following sections illustrate the flaws of Dr. Olson's report.

Reliance on outdated or inadequate reviews of the evidence conducted by others

When offering opinions, Dr. Olson references several reviews conducted by others. In particular, his report contains a large paragraph restating the opinions of the 2009 review by Boucher and coauthors (Boucher et al. 2009). The Boucher et al. review was published more than 10 years ago and therefore excludes a large body of more recent literature. Moreover, even the studies available in 2009 are cited incompletely and often inaccurately. Consider Table 3 (p. 9 of the review) in which Boucher and co-authors attempt to summarize the evidence on the association between PCB exposures and various measures of IQ. They use a downward arrow symbol (↓) to denote a "statistically significant decreased performance on the measure" and a dash (–) to indicate "absence of significant effect." If one were to look at the actual studies included in the table, the selective and inaccurate reporting would become quite obvious. For example, the K-ABC-test results in the Dusseldorf study (Walkowiak et al. 2001) are marked with a downward arrow presumably indicating a significant effect of prenatal exposure. Walkowiak and colleagues indeed reported a significant association between breast milk PCBs and K-ABC but the result was statistically significant only using the one-sided p-value. If the conventional two-sided p-value were used the result would have been not significant. Boucher et al (2009) did not acknowledge that cord blood PCB, a more relevant measure of prenatal exposure, in the Dusseldorf study was unrelated to K-ABC with the association described as "small and even slightly positive."(p. 1604 of the Walkowiak et al. paper). Boucher et al. (2009) also failed to note that the follow up of the Dusseldorf cohort (Winneke et al. 2005), which was already published by the time they conducted their review, observed no association between PCB and K-ABC at 72 months of age. The CPP cohort (Gray et al. 2005) is another example of a study misrepresented in the Boucher et al review. Table 3 denotes the result for the Stanford-Binet test with a dash (–) which is supposed to indicate "absence of significant effect." In fact, the effect was statistically significant, but in the opposite direction; higher PCB levels were associated with better IQ in that study.

Since the publications of the 2009 review the literature has expanded with several recent studies showing no association between PCB exposure and IQ (Berghuis et al. 2018; Drobna et al. 2019; Jacobson et al. 2015; Zhang et al. 2017). Notably, one of those recent studies (Jacobson et al. 2015) was co-authored by one of the authors of the Boucher et al. (2009) review.

Dr. Olson also cites a more recent review by Berghuis and Roze (2019) which asserts that "exposure to PCBs can interfere with normal child development, not only during the perinatal period, but up to and including adolescence." The basis of this assertion is not provided. In fact, the authors of the review also state, in the very next sentence, that "higher prenatal exposure to PCBs was found to be both negatively and positively associated with neurodevelopmental outcomes," which directly contradicts their assertion. It is important to point out that the authors of the review published several articles describing the results of the GIC and RENCO cohort studies. In these studies the authors reported multiple associations that were opposite of the hypothesized direction (for details see pages 40-42 of my report).

Incomplete and erroneous presentation of the original studies

In arriving at his opinions Dr. Olson typically emphasizes publications that support his point of view and usually omits papers that directly contradict his opinion. It addition, when citing a particular study, Dr. Olson tends to mention certain results from that study, again typically ignoring or dismissing the findings that provide data opposing his point of view. Even when citing the results that in his view support his assertions, Dr. Olson sometimes misinterprets these results. These errors are too numerous to count. By way of example, consider the following paragraph from Dr. Olson's report (reproduced verbatim):

Effects of PCBs were detected in infancy on visual recognition memory in several studies (Jacobson et al., 1985; Darvill et al., 2000; Boucher et al., 2014). In most studies, prenatal exposure was associated with adverse effects on cognition in childhood, including poorer IQ scores and response inhibition (Jacobson and Jacobson, 1996, 2003; Stewart et al., 2005). Altered motor development has also been reported, especially gross motor function during infancy as assessed using the Psychomotor Development Index of the Baylay [sic] *Scales of Infant Development (Koopman-Esseboom et al., 1996; Rogan and Gladen, 1991; Walkowiak et al., 2001). Lower psychomotor scores in infants were associated with transplacental (prenatal) PCB exposure in earlier studies by Rogan and Gladen 1991 and Koopman-Esseboom et al., 1996. Detrimental effects of postnatal PCB exposure from breastfeeding was also reported for mental and motor development in children between 7 and 42 months of age (Walkowiak et al., 2001), which were no longer evident when these children were re-assessed at 6 years of age (Winneke et al., 2005). While this may be suggestive of a PCB-related neurodevelopmental delay, it is not supported by the PCB related deficits in IQ in 11-year-old children of the Michigan cohort (Jacobson and Jacobson 1996) and with loss of IQ in 9-year-old children relative to prenatal PCB exposure in the Oswego (Lake Ontario) cohort (Stewart et al., 2008)."*

Each sentence in this paragraph deserves a comment because each sentence contains an error, an important omission, or both. Similar errors and omissions can be found throughout the text, and are not limited to the paragraph in question.

Sentence 1: *"Effects of PCBs were detected in infancy on visual recognition memory in several studies (Jacobson et al., 1985; Darvill et al., 2000; Boucher et al., 2014)."*
Comment: This sentence refers to the results pertaining to the Fagan Test of Infant Intelligence (FTII), which was used in four cohorts – Oswego (Darvill et al. 2000), Michigan (Jacobson et al. 1985), Dusseldorf (Winneke et al. 1998), and Nunavik (Boucher et al. 2014). The four studies

used different exposure measures and thus cannot be compared directly. The only exception is the exposure based on fish consumption which was examined in both Michigan and Oswego cohorts. While the Michigan cohort observed an association between FTII and fish intake, Oswego investigators reported that their analyses "revealed no significant effect of maternal fish consumption" (p. 1036 of the Darvill et al. article). The Dusseldorf cohort study, which found no evidence that FTII was adversely related to PCB exposure is not mentioned at all (Winneke et al. 1998). A more detailed discussion of the FTII results can be found on pages 20-21 of my report.

Sentence 2: *In most studies, prenatal exposure was associated with adverse effects on cognition in childhood, including poorer IQ scores and response inhibition (Jacobson and Jacobson, 1996, 2003; Stewart et al., 2005).*
Comment: The opposite is true. In most reported analyses, prenatal exposure, especially as measured by PCBs in cord blood or maternal blood, was not associated with lower cognition. (Berghuis et al. 2018; Forns et al. 2012c; Gladen and Rogan 1991; Gray et al. 2005; Ikeno et al. 2018; Jacobson et al. 2015; Kyriklaki et al. 2016; Patandin et al. 1999; Tatsuta et al. 2014; Walkowiak et al. 2001; Zhang et al. 2017). Similarly, response inhibition as measured by errors of commission on the CPT or other similar tests was not related to prenatal PCBs in most studies (Boucher et al. 2012a; Jacobson et al. 1992; Neugebauer et al. 2015; Sagiv et al. 2012). Even in the studies cited by Dr. Olson to support his statement, the associations of prenatal PCBs with either cognition or response inhibition were not consistently observed across analyses. Additional details are provided on pages 25-32 of my report.

Sentence 3: *Altered motor development has also been reported, especially gross motor function during infancy as assessed using the Psychomotor Development Index of the Baylay* [sic] *Scales of Infant Development (Koopman-Esseboom et al., 1996; Rogan and Gladen, 1991; Walkowiak et al., 2001).*
Comment: Gross motor function is indeed a component of BSID but it was not specifically examined in either of the three studies cited in the above sentence. Gross motor function was evaluated in three other studies not cited in Dr. Olson's report (Brucker-Davis et al. 2015; Forns et al. 2012c; Pan et al. 2009). None found a statistically significant association with PCBs.

Sentence 4: *Lower psychomotor scores in infants were associated with transplacental (prenatal) PCB exposure in earlier studies by Rogan and Gladen 1991 and Koopman-Esseboom et al., 1996.*
Comment: Koopman-Esseboom et al. evaluated their study participants using BSID at 3, 7 and 18 months of age. Prenatal exposure was characterized as the sum of four PCB congeners (118, 138, 153 and 180) measured in two types of samples – maternal blood and cord blood. A significant association was observed only at 3 months of age and only in relation to maternal blood PCB; no associations were observed with cord blood PCBs at any age or with any exposure at 7 or 18 months of age (Koopman-Esseboom et al. 1996). Rogan and Gladen administered BSID at 18 and 24 months of age. The authors asserted that the result at 24 months of age for PDI was significant; however, a closer inspection of the data indicates that the confidence intervals around the differences between the lowest exposure category and subsequent categories (including the highest) overlapped the null value. More importantly BSID, and specifically BSID-PDI, is one of the very few tests that allow comparison of results across studies that used the same exposure metrics and evaluated participants of similar age.

Table 4 (p. 89 of my report) summarizes the results of age and exposure-specific associations between PCBs and BSID-PDI presented in at least three studies. The table shows that significant results (marked in **bold** for easier identification) are rare and are always in disagreement with other findings.

Sentence 5: *Detrimental effects of postnatal PCB exposure from breastfeeding was also reported for mental and motor development in children between 7 and 42 months of age (Walkowiak et al., 2001), which were no longer evident when these children were re-assessed at 6 years of age (Winneke et al., 2005).*
Comment: In the Dusseldorf cohort (Walkowiak et al. 2001; Wilhelm et al. 2008a; Winneke et al. 1998) mental development was assessed using BSID-MDI and BSID-PDI at the ages of 7, 18 and 30 months. In the earlier study (Winneke et al. 1998) the authors reported "significant negative associations" between PCB in milk and MDI, but the one sided p-value was 0.048, indicating that a conventional two-sided statistical analysis would have produced a p-value of approximately 0.1. The more recent study (Walkowiak et al. 2001) assessed the same associations, but none of the results was statistically significant at 7 months. At 18 and 30 months the results were also not significant based on a conventional two-sided test, as was confirmed in the more recent publication (Wilhelm et al. 2008a); however, they were significant when the results for all three ages were examined together. Motor development was not examined at 42 months of age in any of the Dusseldorf cohort studies; however, it is true that K-ABC results at 42 and 72 months of age differed. More importantly, Dr. Olson fails to consider a large number of other studies that found no consistent association between breast milk PCBs and mental or motor development (Boucher et al. 2014; Brucker-Davis et al. 2015; Darvill et al. 2000; Gladen et al. 1988; Huisman et al. 1995a; Huisman et al. 1995b; Jacobson and Jacobson 1996, 2002a, b, 2003; Jacobson et al. 1985; Kim et al. 2018; Koopman-Esseboom et al. 1996; Lynch et al. 2012; Rogan et al. 1986b; Steuerwald et al. 2000; Wilhelm et al. 2008b). Several of these studies are cited in Dr. Olson's report, but only selected findings are mentioned.

Sentence 6: *While this may be suggestive of a PCB-related neurodevelopmental delay, it is not supported by the PCB related deficits in IQ in 11-year-old children of the Michigan cohort (Jacobson and Jacobson 1996) and with loss of IQ in 9-year-old children relative to prenatal PCB exposure in the Oswego (Lake Ontario) cohort (Stewart et al., 2008)."*
Comment: This sentence appears to include a contradictory statement. It is not clear why in Dr. Olson's opinion "PCB-related neurodevelopmental delay" is "not supported by the PCB-related deficits in IQ". Regardless of the intended meaning of this sentence, it is worth re-emphasizing that analyses demonstrating no evidence of an association between PCBs and IQ outnumber those that reported a statistically significant result. For details, please refer to p. 25-30 of this report.

Interpretation not supported by evidence

Dr. Olson's interpretation of the studies is not based on the evidence presented in these studies. In some instances, Dr. Olson's conclusions even contradict the evidence cited in his own report.

When discussing the results of the CPP cohort, which found no evidence that prenatal PCB exposure is associated with lower IQ (Gray et al. 2005), Dr. Olson seems to attribute this result to confounding. It is important to note, however, that Gray et al. carried out their analyses with

extensive adjustment for confounders, which included "study center (12 categories), maternal age, serum cholesterol, and triglycerides (all continuous), as well as child's sex"; in all models, other factors included in the multivariate analyses were "maternal race, parity, education, socioeconomic index, housing density, smoking status, serum level of heptachlor epoxide, socioeconomic index at the 7-year follow-up, maternal or caregiver education at the 7-year follow-up, maternal or family income at the 7-year follow-up, whether the home emotional environment at the 4-year follow-up was favorable, age in months at the time of the 7-year follow-up, whether meconium was present at birth, and whether the child was breastfed during the hospitalization for delivery" (see p. 19 of Gray et al. 2015).

Similarly, Dr. Olson dismisses the results of the study by Orenstein et al (2014), which found no association between PCB exposure and neurodevelopmental measures such as Visual Memory, Verbal Memory, and Learning, because PCB levels in that study were "much lower than in most other cohorts that reported cognitive deficits." On the other hand, Dr. Olson states (presumably quoting from Schantz et al. 2003): "It is particularly noteworthy that the levels of exposure in some of the more recent studies, the Oswego cohort, for example, are significantly lower than in the earlier studies, yet negative impacts on cognitive functioning are still being reported." It is worth remembering that the range of PCB-153 in the New Bedford, Massachusetts cohort (used in the Orenstein et al. study) was virtually identical to that found in the Oswego cohort, and the levels of PCB-118 may have been higher in New Bedford than in Oswego (Longnecker et al. 2003).

The low levels of exposure in the New Bedford cohort do not stop Dr. Olson from relying on results from the Sagiv et al. (2010) study, which forms the basis for the conclusion that "these findings contribute to a growing literature showing associations between PCBs and children with behavioral problems and/or ADHD-related behavior." However, later in the report Dr. Olson discusses the paper by Forns et al. (2018) and states "In the largest study to date, the authors did not observe any association between either pre- or postnatal exposure (up to 24 months) to PCB-153, p-p_-DDE and HCB and the risk of ADHD before the age of 10 years." Forns et al. (2018) is indeed a large study that needs to be taken into consideration. However, in Dr. Olson's report this study is considered after the conclusions about ADHD is already made.

Summary

Dr. Olson fails to follow the very basic and well-accepted standards of reviewing epidemiologic and other human health studies (Moher et al. 2009; Shea et al. 2007; Simera et al. 2010; Stroup et al. 2000). Concerns about failure to practice sound science has led to the creation of oversight organizations such as The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network, which is described as an international initiative set up to promote "responsible reporting of health research" (Simera et al. 2010). The EQUATOR position statement describes the following practices that "cause major concern"

- Non-reporting or delayed reporting of whole studies
- Selective reporting of only some outcomes in relation to study findings
- The omission of crucial information in the description of research methods and interventions
- Omissions or misinterpretation of results in abstracts
- Inadequate or distorted reporting of harms

- Confusing or misleading presentations of results, data and graphs.

Some of the above areas of concern pertain more specifically to journal articles, but several apply directly to the flaws of Dr. Olson's report.

CONCLUSIONS

This report systematically summarizes the epidemiologic literature on the association between background PCB exposures and neurodevelopmental measures in children of different ages. As evidenced in the report, the literature on the subject is voluminous and spans several decades. The extraordinary amount of published data requires careful evaluation in order to understand and process available information in a systematic fashion.

As discussed earlier in the report, the overall goal of this review was to understand the evidence for and against the hypothesis that PCB exposures at usual levels produce adverse neurodevelopmental effects in children. This overall goal was achieved by seeking answers to the following three questions.

1. Are the same or similar results repeatedly observed and independently reported by different studies conducted in different populations?

The answer to this question is unequivocally "No". The cohorts reviewed in this report collectively evaluated hundreds of different PCB exposure metrics and administered hundreds of different tests (See Appendices I and II). This produced nearly 120,000 possible associations. Yet, the vast majority of these associations were never evaluated or, if evaluated, not reported. Among those that made it into the published literature, about 2,700 were reported only once and thus were never replicated and could not be evaluated with regards to consistency. Just 163 associations were evaluated in at least two cohorts. Not one of those associations was consistently found to be statistically significant across results. Most were consistently non-significant, and for some the results were mixed or conflicting. For example, three cohorts (Dusseldorf, Rotterdam/Groningen and Hokkaido) examined the association between KAB-C and various measures of PCB exposure. The Dutch study observed a statistically significant association with sum of PCBs in maternal and cord blood samples but only among children who were formula fed since birth (Patandin et al. 1999). In the Dusseldorf cohort (Walkowiak et al. 2001) the associations between cord blood PCBs and KAB-C at the same age were described as "small and even slightly positive". On the other hand the association with PCBs measured in children's blood samples was described as statistically significant (although two-sided p-value was exactly 0.05) in Dusseldorf (Walkowiak et al. 2001) but not in the Rotterdam/Groningen study (Patandin et al. 1999). In the Hokkaido cohort only one of 76 associations (between the sum of non-ortho PCBs and the KAB-C mental processing summary scale among boys) was statistically significant and inverse. Several associations, especially for KAB-C achievement scale among Hokkaido girls, were statistically significant, but in the opposite direction (Ikeno et al. 2018). Another study conducted in Japan also administered KAB-C (Tatsuta et al. 2014), but unlike all previous publications, exposure in that article was expressed in terms of PCB homologs rather than congeners. Only the association with one of the ten homolog groups was statistically significant for the overall cognitive scale, but this association was only evident in boys and not in girls. Thus, each study reported an association, but no two associations were the same.

2. Do the same or similar PCB exposures produce effects within the same group of children as these children grow older?

Once again, the answer is "No." A review of the within-cohort data indicates that none of the studies observed a sustained association between PCB and neurodevelopmental measures. This

indicates a lack of coherent pattern. Consider the following example. In the Oswego cohort exposures of interest were initially defined based on reported fish consumption, and cord blood PCBs characterized as total, lightly chlorinated (C11-C13), moderately chlorinated (C14-C16), and highly chlorinated (C17-C19) (Stewart et al. 2000). In the neonatal period the associations with lower test results for some measures were observed for fish consumption and C17-C19 PCB (Stewart et al. 2000). By 6 months of age, the data on fish consumption were no longer reported, and some associations were observed for total, but not C17-C19 PCBs. At 12 months of age the results changed again – some were significant for C17-C19 PCBs but not for total PCBs (Darvill et al. 2000). When the children were 3 years of age, results for total PCBs were no longer reported. There was an association between C17-C19 and MSCA subscales but that association was no longer significant by age 4.5 years (Stewart et al. 2003b). The most recent Oswego cohort publications (Stewart et al. 2008; Stewart et al. 2012) focused on WISC results at the age of 9 and 11 years. No associations were observed with either total or C17-C19 cord blood PCBs but these results are only mentioned briefly in the text. Instead, the authors focused on a different type of sample – placental tissue, and "total PCB" variable was comprised primarily of 118, 138, 153 and 180 congeners. Recall that lightly chlorinated (C11-C13) PCBs (including congeners 118 and 138), and moderately chlorinated (C14-C16) PCBs (including congener 153) were found to be not associated with any of the measures in the neonatal period (Stewart et al. 2000) and were no longer evaluated in any of the subsequent analyses. Thus, these results represent a "moving target" as the reported analyses are continuously changing without providing any evidence of within-cohort consistency.

3. Is there evidence that populations with higher PCB exposure levels experience more adverse neurodevelopmental effects compared to populations with lower exposures?

The data appear to indicate the opposite. Studies with the highest estimated PCB levels were least likely to report statistically significant results. For example, the highest ranked Faroe Islands cohorts found no discernible evidence that PCB is associated with neurodevelopmental test results among newborns or school age children once the results were lipid adjusted or controlled for mercury exposures. The second ranked CPP cohort observed no association between PCB and BSID at 8 months of age, found a statistically significant association, but in the opposite direction, with Stanford-Binet test at 4 years of age, and found no evidence of an association with WISC or WART test results at the age of 7 years. An examination of results across 12 CPP sites shows that the site with the highest PCB levels demonstrated statistically significantly better BSID-PDI scores in relation to higher PCB exposure.

4. Do PCB-exposed children in the general population experience greater incidence of neurodevelopment-related diagnoses?

Once again the answer is 'No'. Although the data on clinical diagnoses such as ADHD and ASD are less voluminous than the data on neurodevelopmental tests, the results are unequivocal. None of the birth cohorts that met the criteria for inclusion in the current report demonstrate any evidence of an association. Studies from Denmark and Norway using comprehensive linkages to their national disease registries did not find an increase in ADHD incidence in relation to PCBs in blood or breast milk samples. The authors of the largest study to-date concluded that they "found no increased risk of ADHD in association with prenatal and early postnatal exposure to PCB-153… in a sample of 4437 children from the general population of seven European birth cohort studies." With respect to ASD, earlier suggestive findings each time were followed by more definitive follow up analyses that found no association. These findings along with data on

opposing trends of PCB levels relative to ASD and ADHD prevalence offer reassurance that these conditions are unrelated to PCB exposure.

In summary, my systematic review of the literature permits the following conclusions:

- Despite hundreds of various exposures and neurodevelopmental measures examined across 35 different populations, the existing body of literature does not report any consistent associations between PCBs and neurodevelopmental function in children.

- The data across and within studies represent a mixture of results in either direction with the majority of findings indicating no significant association.

- There is no evidence that in populations with higher background PCB exposure levels, the association with neurodevelopmental test results is stronger or more commonly observed compared to populations with lower exposures

- The studies of specific neurobehavioral and neurodevelopment conditions such as attention deficit hyperactivity disorder and autism spectrum disorder do not support the proposition that incidence of these conditions is related to PCB exposures.

- Taken together, these observations are reassuring as they offer evidence against a causal relationship between PCBs and neurodevelopmental problems in the general population of children.

In preparation of this report I was also asked to review the expert opinion provided by Dr. James Olson.

- Dr. Olson's opinion that "PCBs cause an increased risk" of neurobehavioral effects "in general population at background, environmental levels of exposure" is based on highly selective and often erroneous evaluation of the published studies. In arriving at this opinion, Dr. Olson failed to follow the most basic guidelines for conducting a systematic review of the literature.

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TABLES AND FIGURES

Figure 1: Summary of Inter-Cohort Consistency: All Exposures

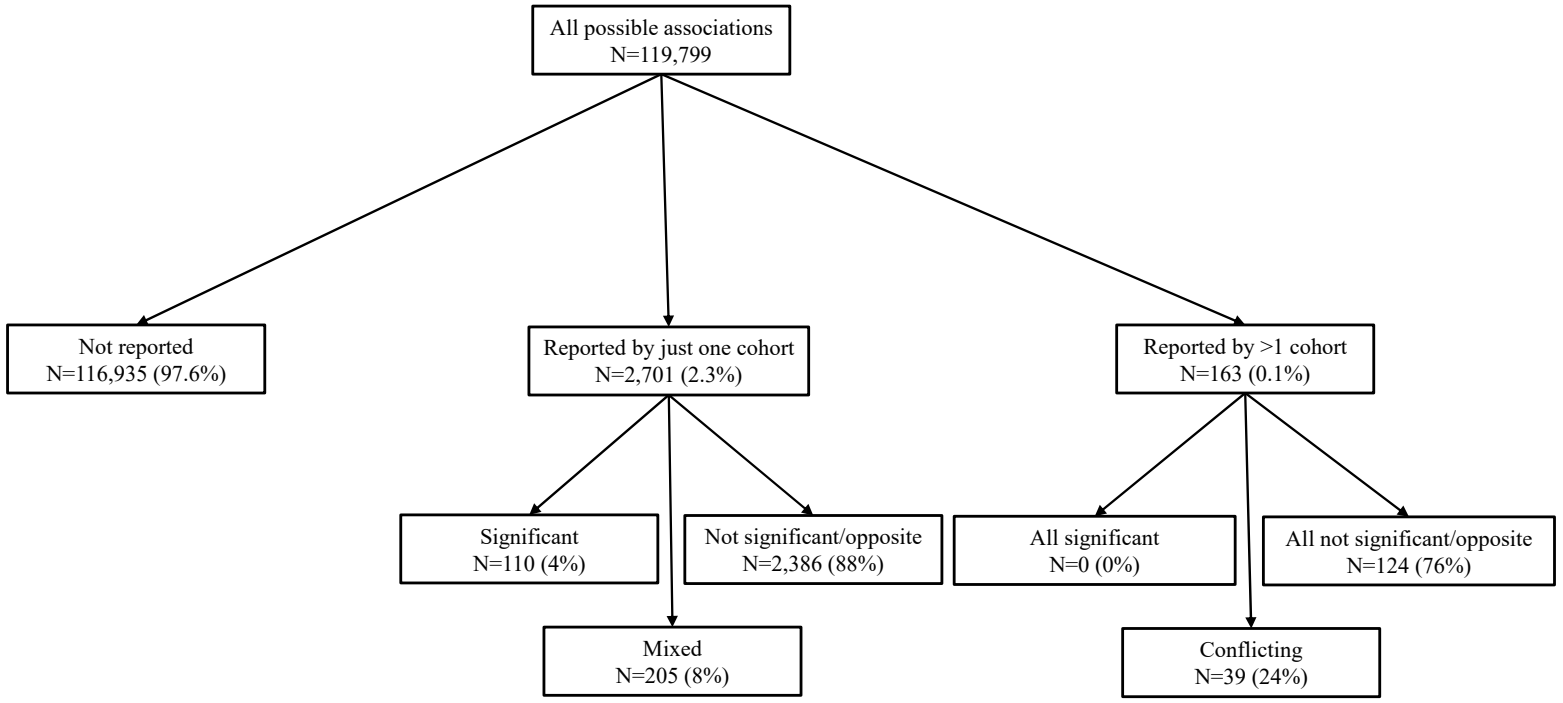

Figure 2: Summary of Inter-Cohort Consistency: Prenatal and Neonatal Exposures

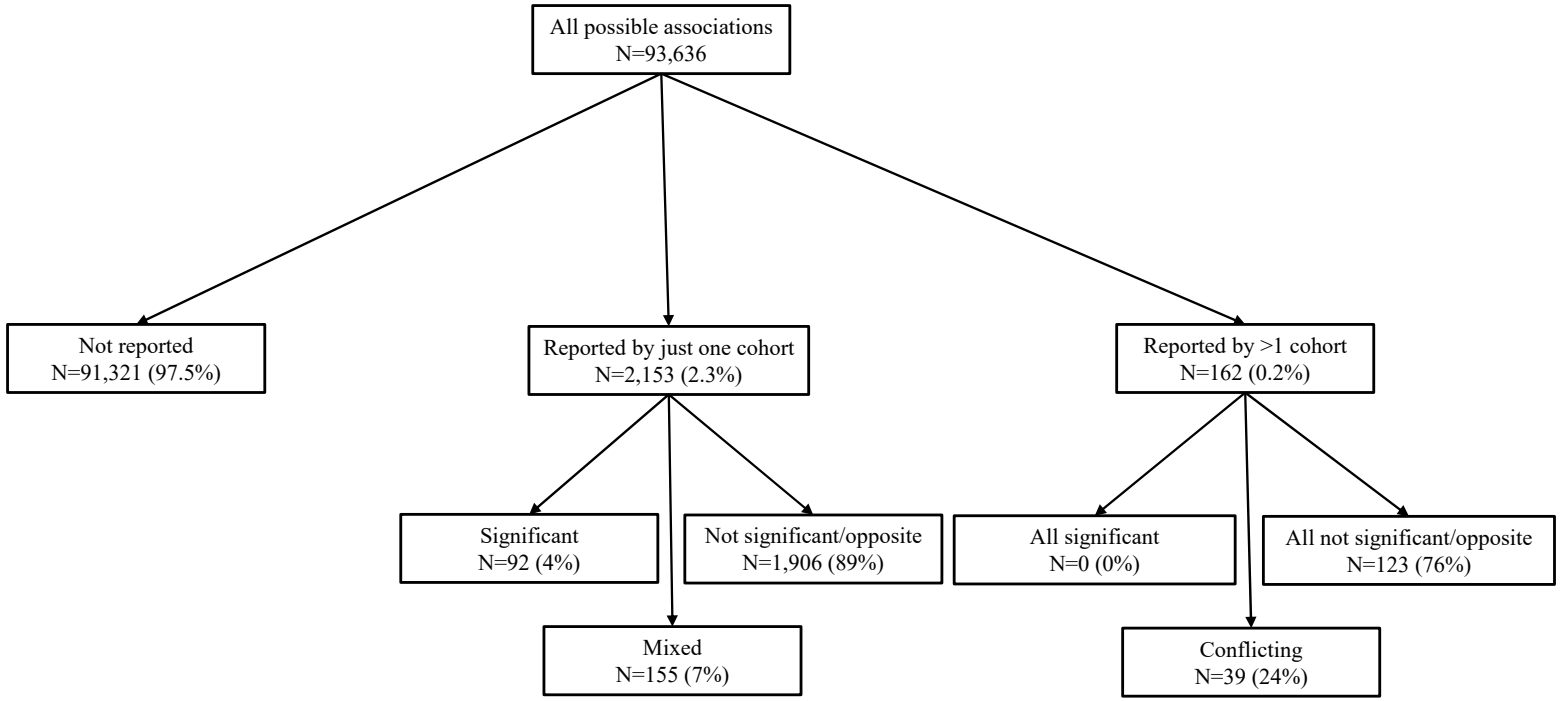

Table 1: Within-Cohort* Reporting and the Likelihood of a Statistically Significant Result: All Exposures

Study Population	Total Exposures	Total Outcomes	Total Associations	Reported		Significant		Mixed	
				Number	%	Number	%	Number	%
Collaborative Perinatal Project, USA	13	21	273	81	30	0	0	1	0
Duisburg, Germany	22	33	726	190	26	5	1	2	0
Dusseldorf, Germany	4	4	16	10	63	0	0	1	6
Eastern Slovakia	64	39	2,496	182	7	16	1	41	2
Faroe Islands 1	8	61	488	180	37	4	1	9	2
GIC, Netherlands	4	31	124	124	100	2	2	6	5
HOME, USA	27	8	216	32	15	0	0	3	1
Hokkaido, Japan	19	4	76	72	95	0	0	11	14
INMA, Spain	19	23	437	96	22	10	2	6	1
Michigan, USA	6	59	354	134	38	10	3	31	9
New Bedford, USA	16	28	448	112	25	11	2	24	5
North Carolina, USA	2	18	36	28	78	0	0	4	11
Nunavik 1, Canada	30	98	2,940	445	15	17	1	17	1
Oswego, USA	11	26	286	105	37	9	3	20	7
RENCO, Netherlands	38	30	1,140	527	46	1	0	15	1
Rotterdam, Netherlands	15	20	300	60	20	3	1	9	3
Rotterdam/Groningen, Netherlands	51	10	510	120	24	14	3	14	3
Tohoku, Japan	15	14	210	67	32	3	1	5	2

* Includes birth cohorts with follow up examinations at two or more different ages

Table 2: Within-Cohort* Reporting and the Likelihood of a Statistically Significant Result: Prenatal And Neonatal Exposures									
Study Population	**Total Exposures**	**Total Outcomes**	**Total Associations**	**Reported**		**Significant**		**Mixed**	
				Number	**%**	**Number**	**%**	**Number**	**%**
Collaborative Perinatal Project, USA	13	21	273	81	30	0	0	1	0
Duisburg, Germany	20	33	660	152	23	3	0	2	0
Dusseldorf, Germany	2	4	8	8	100	0	0	1	13
Eastern Slovakia	34	39	1,326	83	6	14	1	0	0
Faroe Islands 1	7	61	427	163	38	4	1	9	2
GIC, Netherlands	4	31	124	124	100	2	2	6	5
HOME, USA	27	8	216	32	15	0	0	3	1
Hokkaido, Japan	19	4	76	72	95	0	0	11	14
INMA, Spain	14	23	322	63	20	10	3	5	2
Michigan, USA	4	59	236	82	35	10	4	31	13
New Bedford, USA	16	28	448	112	25	11	2	24	5
North Carolina, USA	1	18	18	18	100	0	0	4	22
Nunavik 1, Canada	15	98	1,470	222	15	4	0	9	1
Oswego, USA	11	26	286	105	37	9	3	20	7
RENCO, Netherlands	38	30	1,140	527	46	1	0	15	1
Rotterdam, Netherlands	7	20	140	36	26	3	2	9	6
Rotterdam/Groningen, Netherlands	43	10	430	97	23	14	3	14	3
Tohoku, Japan	15	14	210	67	32	3	1	5	2

* Includes birth cohorts with follow up examinations at two or more different ages

Table 3. Median Levels of PCB Concentrations in Maternal Serum (from Longnecker et al. 2003)			
Study Population	**Estimated Level (ng/g lipid)**		
	*median PCB-153	*Ratio PCB-118/153	median PCB-118**
Faroe Islands	450	0.27	122
CPP	140	0.87	122
Dusseldorf	140	0.20	28
California	130	0.58	75
Michigan	120	0.32	38
Rotterdam/Groningen	100	0.18	18
Nunavik	100	0.14	14
North Carolina	80	0.51	41
Oswego, NY	40	0.23	9
New Bedford, MA	30	0.47	14

*reported in the original article
** calculated

Table 4. Exposure- and Age Interval-Specific Associations between PCBs and BSID-PDI Examined in at Least Three Cohorts

(statistically significant results marked in **bold**)

Exposure	Cohort	Article	Age	Result
Associations examined in 3 different cohorts				
4-OH-PCB-187 in Maternal Blood	Eastern Slovakia	Park et al. 2009	16 mo.	Table 3 (p. 1603): beta = 0.90 (95% CI: –1.90 to 3.70)
	GIC, Netherlands	Ruel et al. 2019	18 mo.	No results included in Table 4. (p. 12). "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12). "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
4-OH-PCB-107 in Maternal Blood	Eastern Slovakia	Park et al. 2009	16 mo.	Table 3 & 4 (p. 1603) beta = –1.66 (95% CI: –5.40 to 2.10)
	GIC, Netherlands	Ruel et al. 2019	18 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
4-OH-PCB-146 in Maternal Blood	Eastern Slovakia	Park et al. 2009	16 mo.	Table 3 (p. 1603): beta = 1.29 (95% CI: –1.55 to 4.14)
	GIC, Netherlands	Ruel et al. 2019	18 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
Associations examined in 4 different cohorts				
PCB 156 in Maternal Blood	Duisburg, Germany	Wilhelm et al. 2008b	12 & 24 mo.	"No adverse effects of dioxins and PCBs at the current background (sampling period 2000-2002) exposure levels in Germany on thyroid function of newborns and their mothers and on neurodevelopment of infants until the age of 24 months were found in the present study." (p. 88)
	Eastern Slovakia	Park et al. 2010	16 mo.	Table 3 (p. 7): **beta = -1.02 (SE = 0.50), p-value <0.05**
	Hokkaido, Japan	Nakajima et al. 2017	18 mo.	Table 3 (p. 226): males, beta = −0.03, p > 0.05; Table 4 (p. 227); females, beta =−0.03, p >0.05
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)

PCB 180 in Maternal Blood	Duisburg, Germany	Wilhelm et al. 2008b	12 & 24 mo.	"No adverse effects of dioxins and PCBs at the current background (sampling period 2000-2002) exposure levels in Germany on thyroid function of newborns and their mothers and on neurodevelopment of infants until the age of 24 months were found in the present study." (p. 88)
	Eastern Slovakia	Park et al. 2010	16 mo.	Table 3 (p. 7): beta = −0.47 (SE = 0.72), p > 0.1
	INMA, Spain	Forns et al. 2012a	18 mo.	Table 4 (p. 75): beta = −0.65 (95% CI: −1.64, 0.34) Supp. Table 3: beta = -0.75 (95% CI: -1.93, 0.43)
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
Associations examined in 5 different cohorts				
PCB 138 in Maternal Blood	CHECK, South Korea	Kim et al. 2018	12-24 mo.	Not included in any of the tables "Only statistically significant results were presented" (footnote Table 3, p. 381). "Only statistically significant results are presented" (footnote Table 4, p. 382)
	Duisburg, Germany	Wilhelm et al. 2008b	12 & 24 mo.	"No adverse effects of dioxins and PCBs at the current background (sampling period 2000-2002) exposure levels in Germany on thyroid function of newborns and their mothers and on neurodevelopment of infants until the age of 24 months were found in the present study." (p. 88)
	Eastern Slovakia	Park et al. 2010	16 mo.	Table 3 (p. 7): beta = -0.53 (SE = 0.70), p > 0.1
	INMA, Spain	Forns et al. 2012a	18 mo.	Table 4 (p. 75): beta = -1.00 (95% CI: −2.03, 0.04); **Supp. Table 3: beta = -1.26 (95% CI: -2.32, -0.20)**
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
Associations examined in 6 different cohorts				
PCB 118 in Maternal Blood	CHECK, South Korea	Kim et al. 2018	12-24 mo.	Not included in any of the tables "Only statistically significant results were presented" (footnote Table 3, p. 381). "Only statistically significant results are presented" (footnote Table 4, p. 382)
	Duisburg, Germany	Wilhelm et al. 2008b	12 & 24 mo.	"No adverse effects of dioxins and PCBs at the current background (sampling period 2000-2002) exposure levels in Germany on thyroid function of newborns and their mothers and on neurodevelopment of infants until the age of 24 months were found in the present study." (p. 88)
	Eastern Slovakia	Park et al. 2010	16 mo.	Table 3 (p. 7): beta = -1.04 (SE = 0.46), p < 0.05
	Hokkaido, Japan	Nakajima et al. 2017	18 mo.	Table 3 (p. 226): males, beta = 0.04, p > 0.05; Table 4 (p. 227); females, beta = 0.04, p > 0.05
	New York Angler Study, USA	Lynch et al. 2012	24 mo.	"Of note, we examined the effect of prenatal exposure to PCBs 118 and 156/171 in our cohort and were unable to replicate this finding (data not shown)." (p. 454)"
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)

Associations examined in 7 different cohorts				
PCB 153 in Maternal Blood	CHECK, South Korea	Kim et al. 2018	12-24 mo.	Not included in any of the tables "Only statistically significant results were presented" (footnote Table 3, p. 381). "Only statistically significant results are presented" (footnote Table 4, p. 382)
	Duisburg, Germany	Wilhelm et al. 2008b	12 & 24 mo.	"No adverse effects of dioxins and PCBs at the current background (sampling period 2000-2002) exposure levels in Germany on thyroid function of newborns and their mothers and on neurodevelopment of infants until the age of 24 months were found in the present study." (p. 88)
	Eastern Slovakia	Park et al. 2010	16 mo.	Table 3 (p. 7): beta = -0.63 (SE = 0.73), p >0.1
	GIC, Netherlands	Ruel et al. 2019	18 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)
	INMA, Spain	Forns et al. 2012a; Gascon et al. 2013	18 mo.	Forns et al. (2012a), Table 4 (p. 75): beta = −0.99 (95% CI: −2.07, 0.09), Supp. Table 3 beta = **-1.50 (95% CI: -2.69, -0.30);** Gascon et al. (2013), Table 2 (p. 12): crude beta = -1.16 (95% CI: -2.41, 0.09), **adj., beta = -1.36 (95% CI: -2.61, -0.11)**
	New York Angler Study, USA	Lynch et al. 2012	24 mo.	Table 3 (p. 454) 2nd vs. 1st tertile: crude beta 10.7 (95% CI: −7.3, 28.7), adj. beta = 16.8 (95% CI: −5.0, 38.6); 3rd vs. 1st tertile crude beta = 12.2 (95% CI: −5.1, 29.7), adj. beta = 14.6 (95% CI: −4.7, 33.9)
	RENCO, Netherlands	Ruel et al. 2019	18 & 30 mo.	No results included in Table 4. (p. 12) "In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test." (p. 8)

APPENDIX 1: LIST OF EXPOSURE CATEGORIES USED IN THE STUDIES OF PCBS AND NEURODEVELOPMENTAL MEASURES

3-OH-PCB-138 In Cord Blood
3-OH-PCB-138 In Maternal Blood
3-OH-PCB-153 In Cord Blood
3-OH-PCB-153 In Maternal Blood
4-OH-PCB-107 In Cord Blood
4-OH-PCB-107 In Maternal Blood
4-OH-PCB-146 In Cord Blood
4-OH-PCB-146 In Maternal Blood
4-OH-PCB-172 In Cord Blood
4-OH-PCB-172 In Maternal Blood
4-OH-PCB-187 In Cord Blood
4-OH-PCB-187 In Maternal Blood
All Measured PCBs In Breastmilk
All Measured PCBs In Breastmilk Or Formula Fat
All Measured PCBs In Breastmilk_Multipollutant Bayesian Model Averaging
All Measured PCBs In Breastmilk_Multipollutant Elastic Net Model
All Measured PCBs In Breastmilk_Multipollutant Principal Component Analysis
All Measured PCBs In Child's Blood
All Measured PCBs In Cord Blood
All Measured PCBs In Maternal Blood
All Measured PCBs In Placental Tissue
All Measured PCBs Teq In Breastmilk
All Measured PCBs Teq In Maternal Blood
Composite Measure Of PCBs In Multiple Samples
Cumulative All Measured PCBs Via Breastmilk
Cumulative Not Specified PCBs Via Breastmilk
Cumulative PCB 153 Via Breastmilk
Cumulative PCBs (118, 138, 153, 180) Via Breastmilk
Cumulative PCBs (138, 153, 180) Via Breastmilk
Cumulative PCBs (Dioxin-Like Teq) Via Breastmilk
Cumulative PCBs (Mono Ortho Teq) Via Breastmilk
Cumulative PCBs (Non Dioxin Like) Via Breastmilk
Cumulative PCBs (Ortho) In Breastmilk
Cumulative PCBs (Planar Teq) Via Breastmilk
Cumulative PCBs Teq Via Breastmilk
Fish Consumption As Surrogate For PCB Exposure
Joint PCBs (118, 138, 153, 180) In Structural Equation Model
Maximum simulated PCB-153 level in first 11 months
Not Specified PCBs In Breastmilk
Not Specified PCBs In Child's Blood

Not Specified PCBs In Cord Blood
Not Specified PCBs In Maternal Blood
PCB 101 In Breastmilk
PCB 101 In Child's Blood
PCB 101 In Cord Blood
PCB 101 In Maternal Blood
PCB 105 In Breastmilk
PCB 105 In Child's Blood
PCB 105 In Cord Blood
PCB 105 In Maternal Blood
PCB 11 In Maternal Blood
PCB 114 In Breastmilk
PCB 114 In Maternal Blood
PCB 118 In Breastmilk
PCB 118 In Child's Blood
PCB 118 In Cord Blood
PCB 118 In Maternal Blood
PCB 118 In Placental Tissue
PCB 123 In Maternal Blood
PCB 126 In Breastmilk
PCB 126 In Maternal Blood
PCB 128 In Breastmilk
PCB 128 In Child's Blood
PCB 128 In Cord Blood
PCB 132 In Maternal Blood
PCB 136 In Maternal Blood
PCB 137 In Breastmilk
PCB 138 In Breastmilk
PCB 138 In Child's Blood
PCB 138 In Cord Blood
PCB 138 In Maternal Blood
PCB 138 In Placental Tissue
PCB 138/158 In Maternal Blood
PCB 141 In Breastmilk
PCB 146 In Cord Blood
PCB 146 In Maternal Blood
PCB 151 In Breastmilk
PCB 153 In Breastmilk
PCB 153 In Child's Blood
PCB 153 In Child's Blood_post-natal average
PCB 153 In Cord Blood
PCB 153 In Maternal Blood
PCB 153 In Placental Tissue

PCB 153 in diet
PCB 153/168 In Breastmilk
PCB 156 In Breastmilk
PCB 156 In Child's Blood
PCB 156 In Cord Blood
PCB 156 In Maternal Blood
PCB 156/171 In Maternal Blood
PCB 157 In Breastmilk
PCB 157 In Maternal Blood
PCB 163 In Child's Blood
PCB 167 In Breastmilk
PCB 167 In Maternal Blood
PCB 169 In Breastmilk
PCB 169 In Maternal Blood
PCB 170 In Breastmilk
PCB 170 In Child's Blood
PCB 170 In Cord Blood
PCB 170 In Maternal Blood
PCB 172 In Maternal Blood
PCB 174 In Maternal Blood
PCB 175 In Maternal Blood
PCB 176 In Maternal Blood
PCB 177 In Breastmilk
PCB 177 In Maternal Blood
PCB 178 In Maternal Blood
PCB 180 In Breastmilk
PCB 180 In Child's Blood
PCB 180 In Cord Blood
PCB 180 In Maternal Blood
PCB 180 In Placental Tissue
PCB 183 In Breastmilk
PCB 183 In Child's Blood
PCB 183 In Cord Blood
PCB 183 In Maternal Blood
PCB 187 In Breastmilk
PCB 187 In Child's Blood
PCB 187 In Cord Blood
PCB 187 In Maternal Blood
PCB 189 In Breastmilk
PCB 189 In Maternal Blood
PCB 194 In Breastmilk
PCB 194 In Maternal Blood
PCB 195 In Breastmilk

PCB 195 In Maternal Blood
PCB 196 In Maternal Blood
PCB 196/203 In Maternal Blood
PCB 199 In Maternal Blood
PCB 202 In Breastmilk
PCB 203 In Maternal Blood
PCB 206 In Cord Blood
PCB 206 In Maternal Blood
PCB 207 In Cord Blood
PCB 208 In Cord Blood
PCB 209 In Maternal Blood
PCB 28 In Breastmilk
PCB 28 In Cord Blood
PCB 28 In Maternal Blood
PCB 52 In Breastmilk
PCB 52 In Cord Blood
PCB 52 In Maternal Blood
PCB 66 In Breastmilk
PCB 66 In Maternal Blood
PCB 70 In Breastmilk
PCB 74 In Breastmilk
PCB 74 In Maternal Blood
PCB 77 In Breastmilk
PCB 77 In Maternal Blood
PCB 84 In Maternal Blood
PCB 91 In Maternal Blood
PCB 95 In Maternal Blood
PCB 99 In Breastmilk
PCB 99 In Child's Blood
PCB 99 In Cord Blood
PCB 99 In Maternal Blood
Postnatal PCB 153 at 0-3 months_system model
Postnatal PCB 153 at 0-6 months_system model
Postnatal PCB 153 at 1 month_pharmacokinetic model
Postnatal PCB 153 at 10 months_pharmacokinetic model
Postnatal PCB 153 at 11 months_pharmacokinetic model
Postnatal PCB 153 at 12 months_pharmacokinetic model
Postnatal PCB 153 at 12-15 months_system model
Postnatal PCB 153 at 12-18 months_system model
Postnatal PCB 153 at 15-18 months_system model
Postnatal PCB 153 at 18-21 months_system model
Postnatal PCB 153 at 18-24 months_system model
Postnatal PCB 153 at 2 months_pharmacokinetic model

Postnatal PCB 153 at 21-24 months_system model
Postnatal PCB 153 at 24 months_pharmacokinetic model
Postnatal PCB 153 at 24-27 months_system model
Postnatal PCB 153 at 24-30 months_system model
Postnatal PCB 153 at 27-30 months_system model
Postnatal PCB 153 at 3 months_pharmacokinetic model
Postnatal PCB 153 at 3-6 months_system model
Postnatal PCB 153 at 30-33 months_system model
Postnatal PCB 153 at 30-36 months_system model
Postnatal PCB 153 at 33-36 months_system model
Postnatal PCB 153 at 36-39 months_system model
Postnatal PCB 153 at 36-42 months_system model
Postnatal PCB 153 at 39-42 months_system model
Postnatal PCB 153 at 4 months_pharmacokinetic model
Postnatal PCB 153 at 42-45 months_system model
Postnatal PCB 153 at 42-48 months_system model
Postnatal PCB 153 at 48-54 months_system model
Postnatal PCB 153 at 5 months_pharmacokinetic model
Postnatal PCB 153 at 54-60 months_system model
Postnatal PCB 153 at 6 months_pharmacokinetic model
Postnatal PCB 153 at 6-12 months_system model
Postnatal PCB 153 at 6-9 months_system model
Postnatal PCB 153 at 60-66 months_system model
Postnatal PCB 153 at 66-72 months_system model
Postnatal PCB 153 at 7 months_pharmacokinetic model
Postnatal PCB 153 at 8 months_pharmacokinetic model
Postnatal PCB 153 at 9 months_pharmacokinetic model
Postnatal PCB 153 at 9-12 months_system model
Simulated cord blood PCB 153
Sum 1 CB Homologs in Cord Blood
Sum 10 CB Homologs in Cord Blood
Sum 2 CB Homologs in Cord Blood
Sum 3 CB Homologs In Cord Blood
Sum 4 CB Homologs In Cord Blood
Sum 5 CB Homologs In Cord Blood
Sum 6 CB Homologs In Cord Blood
Sum 7 CB Homologs In Cord Blood
Sum 8 CB Homologs In Cord Blood
Sum 9 CB Homologs In Cord Blood
Sum Of OH-PCBs In Cord Blood
Sum Of OH-PCBs In Maternal Blood
Sum PCBs (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) In Cord Blood
Sum PCBs (105, 118, 138, 146, 153, 156, 170, 180, 183, 187) In Maternal Blood

Sum PCBs (105, 118, 156 Teq) In Breastmilk
Sum PCBs (105, 118, 156) In Maternal Blood
Sum PCBs (105, 118, 156, 167, 189 Teq) In Cord Blood
Sum PCBs (11, 52, 77, 84, 91, 95, 101, 118, 132, 136, 138, 153, 174, 175, 176, 180, 196) In Maternal Blood
Sum PCBs (118, 138, 153 180) in Breastmilk
Sum PCBs (118, 138, 153, 156, 170, 180) In Maternal Blood
Sum PCBs (118, 138, 153, 170, 180, 187) In Maternal Blood
Sum PCBs (118, 138, 153, 180) In Breastmilk
Sum PCBs (118, 138, 153, 180) In Child's Blood
Sum PCBs (118, 138, 153, 180) In Cord Blood
Sum PCBs (118, 138, 153, 180) In Maternal Blood
Sum PCBs (118, 156) In Breastmilk
Sum PCBs (118, 156) In Cord Blood
Sum PCBs (118, 156) In Maternal Blood
Sum PCBs (138, 146, 153, 170, 180, 183, 187) In Maternal Blood
Sum PCBs (138, 153, 170, 180) In Cord Blood
Sum PCBs (138, 153, 170, 180) In Maternal Blood
Sum PCBs (138, 153, 180) In Breastmilk
Sum PCBs (138, 153, 180) In Child's Blood
Sum PCBs (138, 153, 180) In Cord Blood
Sum PCBs (138, 153, 180) In Cord Tissue
Sum PCBs (138, 153, 180) In Maternal Blood
Sum PCBs (138, 156, 170, 180) In Cord Blood
Sum PCBs (138, 156, 170, 180) In Maternal Blood
Sum PCBs (170, 180 Teq) In Breastmilk
Sum PCBs (28, 118, 138, 153) in Maternal Blood
Sum PCBs (28, 52, 101, 118, 138, 153, 180) In Cord Blood
Sum PCBs (28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) In Maternal Blood
Sum PCBs (52, 84, 95, 136, 176) In Maternal Blood
Sum PCBs (74, 105, 118, 138, 153, 170, 180) In Maternal Blood
Sum PCBs (74, 99, 118, 138, 153, 156, 170, 180, 183, 187) In Maternal Blood
Sum PCBs (77, 118) In Maternal Blood
Sum PCBs (77, 126) In Breastmilk
Sum PCBs (77, 126, 169 Teq) In Breastmilk
Sum PCBs (C11 C13) In Cord Blood
Sum PCBs (C14 C16) In Cord Blood
Sum PCBs (C17 C19) In Cord Blood
Sum PCBs (Coplanar Teq) In Maternal Blood
Sum PCBs (Coplanar) In Maternal Blood
Sum PCBs (Dioxin-Like TEQ) In Maternal Blood
Sum PCBs (Dioxin-Like Teq) In Breastmilk
Sum PCBs (Dioxin-Like Teq) In Maternal Blood
Sum PCBs (Mono Ortho Teq) In Maternal Blood

Sum PCBs (Mono Ortho) In Maternal Blood
Sum PCBs (NEQ) In Maternal Blood
Sum PCBs (Non Dioxin Like) In Breastmilk
Sum PCBs (Non Ortho Teq) In Maternal Blood
Sum PCBs (Non Ortho) In Maternal Blood
Sum PCBs (thyroid hormone-based TEQ) In Maternal Blood

APPENDIX 2: LIST OF DEPENDENT VARIABLES USED IN THE STUDIES OF PCBS AND NEURODEVELOPMENTAL MEASURES

300ms Auditory Event Related Brain Potential_Amplitudes Cz
300ms Auditory Event Related Brain Potential_Amplitudes Fz
300ms Auditory Event Related Brain Potential_Amplitudes Pz
300ms Auditory Event Related Brain Potential_Latencies Cz
300ms Auditory Event Related Brain Potential_Latencies Fz
300ms Auditory Event Related Brain Potential_Latencies Pz
A-Not-B_Length Of Delay 2 Correct
A-Not-B_Length Of Delay 3 Correct
A-Not-B_Percent Perseverative Errors
ADHD questionnaire
Age Of Crawling
Age Of Standing-up
Age Of Walking
Ages and Stages Questionnaires_Low vs. High Communication Skills Score
Alternating Movement Outcome_Coefficient Of Variation
Alternating Movement Outcome_Coherence Between Hands
Alternating Movement Outcome_Synkinesis
Antigravity Movements
Attention Deficit Hyperactivity Disorder
Auditory Evoked Potential Latencies_20 Hz_Peak I
Auditory Evoked Potential Latencies_20 Hz_Peak I-III
Auditory Evoked Potential Latencies_20 Hz_Peak III
Auditory Evoked Potential Latencies_20 Hz_Peak III-V
Auditory Evoked Potential Latencies_20 Hz_Peak V
Auditory Evoked Potential Latencies_40 Hz_Peak I
Auditory Evoked Potential Latencies_40 Hz_Peak I-III
Auditory Evoked Potential Latencies_40 Hz_Peak III
Auditory Evoked Potential Latencies_40 Hz_Peak III-V
Auditory Evoked Potential Latencies_40 Hz_Peak V
Auditory Oddball Test Event Related Potentials_ N1 Amplitude Standard Condition
Auditory Oddball Test Event Related Potentials_ N1 Amplitude Target Condition
Auditory Oddball Test Event Related Potentials_ N1 Latency Standard Condition
Auditory Oddball Test Event Related Potentials_ N1 Latency Target Condition
Auditory Oddball Test Event Related Potentials_ P3b Amplitude Standard Condition
Auditory Oddball Test Event Related Potentials_ P3b Amplitude Target Condition
Auditory Oddball Test Event Related Potentials_ P3b Latency Standard Condition
Auditory Oddball Test Event Related Potentials_ P3b Latency Target Condition
Auditory Oddball Test_Errors Of Commission
Auditory Oddball Test_Errors Of Omission
Auditory Oddball Test_Reaction Time

Auditory Threshold_1000 Hz_Left Ear
Auditory Threshold_1000 Hz_Right Ear
Auditory Threshold_12000 Hz_Left Ear
Auditory Threshold_12000 Hz_Right Ear
Auditory Threshold_125 Hz_Left Ear
Auditory Threshold_125 Hz_Right Ear
Auditory Threshold_2000 Hz_Left Ear
Auditory Threshold_2000 Hz_Right Ear
Auditory Threshold_250 Hz_Left Ear
Auditory Threshold_250 Hz_Right Ear
Auditory Threshold_4000 Hz_Left Ear
Auditory Threshold_4000 Hz_Right Ear
Auditory Threshold_500 Hz_Left Ear
Auditory Threshold_500 Hz_Right Ear
Auditory Threshold_8000 Hz_Left Ear
Auditory Threshold_8000 Hz_Right Ear
Auditory Verbal Learning Test_Delayed Recognition
Auditory Verbal Learning Test_Long Term Memory Score
Auditory Verbal Learning Test_Not Specified
Auditory Verbal Learning Test_Short Term Memory Score
Autism Diagnostic Observation Schedule
Autism Spectrum Disorder
Ballard Examination For Fetal Maturity_Neuromuscular Maturity
Bayley Scale Of Infant Development_Mental Development Index
Bayley Scale Of Infant Development_Psychomotor Development Index
Bayley Scales Of Infant Development_Emotional Regulation
Bayley Scales Of Infant Development_Motor Quality
Bayley Scales Of Infant Development_Orientation/Engagement
Bayley Scales Of Infant Development_Total Behavior Rating
Bayley Scales Of Infant and Toddler Development_Cognitive
Bayley Scales Of Infant and Toddler Development_Expressive Language
Bayley Scales Of Infant and Toddler Development_Fine Motor
Bayley Scales Of Infant and Toddler Development_Gross Motor
Bayley Scales Of Infant and Toddler Development_Language
Bayley Scales Of Infant and Toddler Development_Motor
Bayley Scales Of Infant and Toddler Development_Receptive Language
Bayley Scales Of Infant and Toddler Development_Social Emotional
Beery Test Of Visual-Motor Impairment
Behavior Rating Inventory Of Executive Function_ Working memory
Behavior Rating Inventory Of Executive Function_Emotional Control
Behavior Rating Inventory Of Executive Function_Inhibition
Behavior Rating Inventory Of Executive Function_Planning and organizing
Behavior Rating Inventory Of Executive Function_Shift

Behavioral Assessment System for Children-2_ Externalizing Problems
Bender Visual Motor Gestalt Test_Errors On Copying
Bender Visual Motor Gestalt Test_Reproduction
Boston Naming Test_No Cues Score
Boston Naming Test_With Cues Score
California Verbal Learning Test_Learning
California Verbal Learning Test_Long Term Recall
California Verbal Learning Test_Recognition
California Verbal Learning Test_Short Term Recall
Child Behavior Checklist_Attention Problems
Child Behavior Checklist_Externalizing Score
Child Behavior Checklist_Externalizing Score_Parents
Child Behavior Checklist_Externalizing Score_Teachers
Child Behavior Checklist_Internalizing Score
Child Behavior Checklist_Internalizing Score_Parents
Child Behavior Checklist_Internalizing Score_Teachers
Child Behavior Checklist_Sleep Problems
Child Behavior Checklist_Total Score
Child Behavior Checklist_Total Score_Parents
Child Behavior Checklist_Total Score_Teachers
Child Behavior Ratings_Activity
Child Behavior Ratings_Anxiety
Child Behavior Ratings_Attentiveness
Child Behavior Ratings_Cooperation
Child Behavior Ratings_Energy
Child Behavior Ratings_Impulsivity
Child Behavior Ratings_Social Ease
Child Development Inventory_Expressive Language
Child Hyperactivity Problems
Computerized Test Battery For Attentional Performance For Children (KITAP)_Alertness_Errors Of Omission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Alertness_Reaction Time
Computerized Test Battery For Attentional Performance For Children (KITAP)_Distractibility_Errors Of Commission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Distractibility_Errors Of Omission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Distractibility_Reaction Time
Computerized Test Battery For Attentional Performance For Children (KITAP)_Divided Attention_Errors Of Commission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Divided Attention_Errors Of Omission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Divided Attention_Reaction time
Computerized Test Battery For Attentional Performance For Children (KITAP)_Flexibility_Errors Of Commission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Flexibility_Reaction Time
Computerized Test Battery For Attentional Performance For Children (KITAP)_Go/Nogo_Errors Of Commission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Go/Nogo_Errors Of Omission
Computerized Test Battery For Attentional Performance For Children (KITAP)_Go/Nogo_Reaction Time
Computerized Test Battery For Attentional Performance For Children (KITAP)_Performance Quality

Computerized Test Battery For Attentional Performance For Children (KITAP)_Performance Speed
Conners' Rating Scale For Teachers_ADHD Index
Conners' Rating Scale For Teachers_Hyperactive-Impulsive
Conners' Rating Scale For Teachers_Inattentive
Conners' Rating Scale For Teachers_Total
Continuous Performance Test_Errors Of Commission
Continuous Performance Test_Errors Of Omission
Continuous Performance Test_Number Correct
Continuous Performance Test_Reaction Time
Continuous Performance Test_Reaction Time Variability
Contrast Sensitivity_1.5 Cycles Per Degree Left Eye
Contrast Sensitivity_1.5 Cycles Per Degree Right Eye
Contrast Sensitivity_12 Cycles Per Degree Left Eye
Contrast Sensitivity_12 Cycles Per Degree Right Eye
Contrast Sensitivity_18 Cycles Per Degree Left Eye
Contrast Sensitivity_18 Cycles Per Degree Right Eye
Contrast Sensitivity_3 Cycles Per Degree Left Eye
Contrast Sensitivity_3 Cycles Per Degree Right Eye
Contrast Sensitivity_6 Cycles Per Degree Left Eye
Contrast Sensitivity_6 Cycles Per Degree Right Eye
Corsi Spatial Span
Depression
Developmental Coordination Disorder Questionnaire
Developmental Coordination Disorder Questionnaire Score
Differential Reinforcement Of Low Rates_Interresponse Times
Differential Reinforcement Of Low Rates_Total Reinforced Responses
Digit Cancelation Test_Errors Of Omission
Disruptive Behavior Disorders Rating Scale_ADHD_Hyperactive_Impulsive Type
Disruptive Behavior Disorders Rating Scale_ADHD_Inattentive Type
Disruptive Behavior Disorders Rating Scale_Oppositional Defiant and/or Conduct Disorder
Distortion Product Otoacoustic Emissions Growth_45 dB
Distortion Product Otoacoustic Emissions Growth_50 dB
Distortion Product Otoacoustic Emissions Growth_55 dB
Distortion Product Otoacoustic Emissions Growth_60 dB
Distortion Product Otoacoustic Emissions Growth_65 dB
Distortion Product Otoacoustic Emissions Growth_70 dB
Distortion Product Otoacoustic Emissions Growth_75 dB
Distortion Product Otoacoustic Emissions_1000 Hz
Distortion Product Otoacoustic Emissions_1189 Hz
Distortion Product Otoacoustic Emissions_1414 Hz
Distortion Product Otoacoustic Emissions_1682 Hz
Distortion Product Otoacoustic Emissions_2000 Hz
Distortion Product Otoacoustic Emissions_2378 Hz

Distortion Product Otoacoustic Emissions_2828 Hz
Distortion Product Otoacoustic Emissions_3364 Hz
Distortion Product Otoacoustic Emissions_4000 Hz
Distortion Product Otoacoustic Emissions_4757 Hz
Distortion Product Otoacoustic Emissions_5657 Hz
Distortion Product Otoacoustic Emissions_Left Ear
Distortion Product Otoacoustic Emissions_Overall
Distortion Product Otoacoustic Emissions_Right Ear
Empathy Quotient
Extended Continuous Performance Test_Response Accuracy
Fagan Test Of Infant Intelligence_Fixation Score
Fagan Test Of Infant Intelligence_Novelty Score
Finger Tapping Test_Dominant Hand Score
Finger Tapping Test_Other Hand Score
Finger Tapping Test_Total Score
Fluency Cluster Score
Grades_English
Grades_Math
Grammar Rating_Incomplete Grammar
Grammar Rating_Moderate Language Delay
Grammar Rating_Severe Language Delay
Grammar Rating_Speech Problems
Griffiths Mental Development Scales_Eye-Hand Coordination
Griffiths Mental Development Scales_Hearing and Language
Griffiths Mental Development Scales_Locomotor
Griffiths Mental Development Scales_Performance
Griffiths Mental Development Scales_Personal-Social
Hand-Eye Coordination Test
Infant Behavior Rating Scale_Activity
Infant Behavior Rating Scale_Anxiety
Infant Behavior Rating Scale_Attention
Infant Behavior Rating Scale_Cooperation
Infant Behavior Rating Scale_Emotional Tone
Infant Behavior Rating Scale_Impulsivity
Infant Behavior Rating Scale_Irritability
Infant Behavior Rating Scale_Social Ease
Infant/Toddler Symptom Checklist _Total Score
Inhibitory control
Kaufman Assessment Battery For Children_Achievement Scale
Kaufman Assessment Battery For Children_Overall Cognitive Scale/Mental Processing Composite
Kaufman Assessment Battery For Children_Sequential Processing Scale Score
Kaufman Assessment Battery For Children_Simultaneous Processing Scale Score
Macarthur-Bates Communicative Development Inventories Score

Manipulation
McCarthy Scales Of Children's Abilities_Block Building Subtest
McCarthy Scales Of Children's Abilities_Draw-a-Design Subtest
McCarthy Scales Of Children's Abilities_Executive Function Subscale
McCarthy Scales Of Children's Abilities_Fine Motor Ability Subscale
McCarthy Scales Of Children's Abilities_General Cognitive
McCarthy Scales Of Children's Abilities_Gross Motor Ability Subscale
McCarthy Scales Of Children's Abilities_Memory
McCarthy Scales Of Children's Abilities_Memory Span Subscale
McCarthy Scales Of Children's Abilities_Motor
McCarthy Scales Of Children's Abilities_Perceptual_Performance
McCarthy Scales Of Children's Abilities_Posterior Cortex Subscale
McCarthy Scales Of Children's Abilities_Quantitative
McCarthy Scales Of Children's Abilities_Verbal
McCarthy Scales Of Children's Abilities_Verbal Memory Subscale
McCarthy Scales Of Children's Abilities_Word Knowledge Subtest
McCarthy Scales Of Children's Abilities_Working Memory Subscale
Mental Rotation Backward_Reaction Time
Mental Rotation Forward_Reaction Time
Mental Rotation_Number Correct
Mental Rotation_Reaction Time
Midline Arm Movements
Midline Leg Movements
Motor Optimality Score
Motor-Related Deficits
Movement Assessment Battery For Children_Ball Skills
Movement Assessment Battery For Children_Fine Motor Skills
Movement Assessment Battery For Children_Static And Dynamic Balance
Movement Assessment Battery For Children_Total Motor Skills
Movement Character_Cramped
Movement Character_Cramped-Synchronized
Movement Character_Jerky
Movement Character_Monotonous
Movement Character_Stiff
Movement Character_Tremulous
Mullen Scales Of Early Learning_Composite Standard Score
Mullen Scales Of Early Learning_Expressive
Mullen Scales Of Early Learning_Fine Motor
Mullen Scales Of Early Learning_Gross Motor
Mullen Scales Of Early Learning_Non_Typical Development
Mullen Scales Of Early Learning_Receptive
Mullen Scales Of Early Learning_Visual
Neonatal Behavioral Assessment Scale _ Consolability

Neonatal Behavioral Assessment Scale _ Alertness
Neonatal Behavioral Assessment Scale _ Autonomic Maturity
Neonatal Behavioral Assessment Scale _ Cost Of Attention
Neonatal Behavioral Assessment Scale _ Elicited Activity
Neonatal Behavioral Assessment Scale _ Failure To Recover
Neonatal Behavioral Assessment Scale _ Hand_To_Mouth
Neonatal Behavioral Assessment Scale _ Irritability
Neonatal Behavioral Assessment Scale _ Low Reflexes Subscore
Neonatal Behavioral Assessment Scale _ Motor Maturity
Neonatal Behavioral Assessment Scale _ Never In State To Do Orientation Items
Neonatal Behavioral Assessment Scale _ Orientation
Neonatal Behavioral Assessment Scale _ Quality Of Alertness
Neonatal Behavioral Assessment Scale _ Range Of State
Neonatal Behavioral Assessment Scale _ Reflexes
Neonatal Behavioral Assessment Scale _ Regulation Of State
Neonatal Behavioral Assessment Scale _ Response Decrement
Neonatal Behavioral Assessment Scale _ Self_Quieting
Neonatal Behavioral Assessment Scale _ Spontaneous Activity
Neonatal Behavioral Assessment Scale _ Tonicity
Neonatal Behavioral Assessment Scale_Percent Poor Scores
Neurologic Optimality Score
Neurologic Optimality Score _ Muscle Postural Tone
Neurologic Optimality Score _ Reflexes
Neurologic Optimality Score_Sensorimotor Function
Neurologic Optimality Score_Visuomotor Function
Observed Behavior_ Legs Activity Duration
Observed Behavior_ Off Task Duration
Observed Behavior_ Positive Affect Rate
Observed Behavior_ Vocalization
Observed Behavior_Global Activity Latency
Observed Behavior_Global Activity Rate
Observed Behavior_Inattenton Duration
Observed Behavior_Inattenton Rate
Observed Behavior_Non-Elicited Activity Duration
Observed Behavior_Non-Elicited Activity Rate
Observed Behavior_Off Task Latency
Parent Rating Scale For Attention Deficit Hyperactivity Disorder_Hyperactivity
Parent Rating Scale For Attention Deficit Hyperactivity Disorder_Impulsivity
Parent Rating Scale For Attention Deficit Hyperactivity Disorder_Inattention
Parent Rating Scale For Attention Deficit Hyperactivity Disorder_Overall ADHD
Peabody Picture Vocabulary Test
Posner Attention_Shift Paradigm Test_ Accuracy
Posner Attention_Shift Paradigm Test_ Errors Of Commission

Posner Attention_Shift Paradigm Test_ Errors Of Omission
Posner Attention_Shift Paradigm Test_ Reaction Time
Posner Attention_Shift Paradigm Test_Validity Effect
Pre School Activity Inventory _ Feminine
Pre School Activity Inventory _Composite
Pre School Activity Inventory _Masculine
Preschool Age Psychiatric Assessment _ Impulsivity
Preschool Age Psychiatric Assessment_ADHD score
Preschool Age Psychiatric Assessment_Hyperactivity
Preschool Age Psychiatric Assessment_Inattention
Pure Tone Audiometry_1000 Hz
Pure Tone Audiometry_125 Hz
Pure Tone Audiometry_2000 Hz
Pure Tone Audiometry_250 Hz
Pure Tone Audiometry_4000 Hz
Pure Tone Audiometry_500 Hz
Pure Tone Audiometry_8000 Hz
Quality Of Fidgety Movements
Reaction Time
Repertoire Of Co-existent Other Movements
Rey Complex Figure Test_Copy
Rey Complex Figure Test_Copy Strategy
Rey Complex Figure Test_Recall
Santa Ana Alternation Hands Subscore
Santa Ana Dominant Hand Subscore
Santa Ana Other Hand Subscore
Santa Ana Total
Scholastic Achievement
Seashore Rhythm Test
Selective Visual Attention
Simple Reaction Time Test_Response Time
Simple Reaction Time Test_The Variation In Response Time
Social Maturity Scale_Social Quotient
Social Responsiveness Scale_Autistic Mannerisms
Social Responsiveness Scale_Overall
Social Responsiveness Scale_Restricted Interests And Repetitive Behaviour
Social Responsiveness Scale_Social Awareness
Social Responsiveness Scale_Social Cognition
Social Responsiveness Scale_Social Communication
Social Responsiveness Scale_Social Motivation
Stanford-Binet_Copying Subtest
Stanford-Binet_Non-Verbal IQ
Stanford-Binet_Non-Verbal Working Memory

Stanford-Binet_Total IQ
Stanford-Binet_Verbal IQ
Stanford-Binet_Verbal Working Memory
Stanford-Binet_Working Memory Index
Sternberg Memory_Errors Of Commission
Sternberg Memory_Number Correct
Sternberg Memory_Reaction Time
Sternberg Memory_Total Errors
Strengths and Difficulties Questionnaire_Conduct problems
Strengths and Difficulties Questionnaire_Emotional Symptoms
Strengths and Difficulties Questionnaire_Hyperactive Symptoms
Strengths and Difficulties Questionnaire_Inattentive Symptoms
Strengths and Difficulties Questionnaire_Peer Problems
Strengths and Difficulties Questionnaire_Prosocial Behavior
Strengths and Difficulties Questionnaire_Total Difficulties
Stroop Color Word Test
Sustained Auditory Attention
Sway Analysis Test System_Sagittal Sway In Balance Condition
Sway Analysis Test System_Sagittal Sway In Static Condition
Sway Analysis Test System_Transversal Sway In Balance Condition
Sway Analysis Test System_Velocity Sway In Static Condition
Systemizing Quotient
Towen's Neurologic Examination_ Sensory Integration
Towen's Neurologic Examination_ Tremors
Towen's Neurologic Examination_Choreiform Dyskinesia
Towen's Neurologic Examination_Coordination
Towen's Neurologic Examination_Fine Manipulative Abilities
Tower Of London
Tremor
Verbal Comprehension Scale Of The Reynell Developmental Language Scales
Verbally-Mediated Deficits
Vigilance Composite Measure
Visual Discrimination Task_Number Correct
Visual Discrimination Task_Reaction Time
Visual Evoked Potential Amplitude_12% Contrast N150
Visual Evoked Potential Amplitude_12% Contrast N75
Visual Evoked Potential Amplitude_12% Contrast N75 To P101
Visual Evoked Potential Amplitude_12% Contrast P100 To N151
Visual Evoked Potential Amplitude_12% Contrast P101
Visual Evoked Potential Amplitude_30% Contrast N150
Visual Evoked Potential Amplitude_30% Contrast N75
Visual Evoked Potential Amplitude_30% Contrast N75 To P101
Visual Evoked Potential Amplitude_30% Contrast P100 To N151

Visual Evoked Potential Amplitude_30% Contrast P101
Visual Evoked Potential Amplitude_4% Contrast N150
Visual Evoked Potential Amplitude_4% Contrast N75
Visual Evoked Potential Amplitude_4% Contrast P101
Visual Evoked Potential Amplitude_95% Contrast N150
Visual Evoked Potential Amplitude_95% Contrast N75
Visual Evoked Potential Amplitude_95% Contrast N75 To P101
Visual Evoked Potential Amplitude_95% Contrast P100 To N151
Visual Evoked Potential Amplitude_95% Contrast P101
Visual Evoked Potential Latencies_Arc Width 15' N145
Visual Evoked Potential Latencies_Arc Width 15' N75
Visual Evoked Potential Latencies_Arc Width 15' P101
Visual Evoked Potential Latencies_Arc Width 30' N145
Visual Evoked Potential Latencies_Arc Width 30' N75
Visual Evoked Potential Latencies_Arc Width 30' P101
Visual Evoked Potential Latency_12% Contrast N150
Visual Evoked Potential Latency_12% Contrast N75
Visual Evoked Potential Latency_12% Contrast P101
Visual Evoked Potential Latency_30% Contrast N150
Visual Evoked Potential Latency_30% Contrast N75
Visual Evoked Potential Latency_30% Contrast P101
Visual Evoked Potential Latency_4% Contrast N150
Visual Evoked Potential Latency_4% Contrast N75
Visual Evoked Potential Latency_4% Contrast P101
Visual Evoked Potential Latency_95% Contrast N150
Visual Evoked Potential Latency_95% Contrast N75
Visual Evoked Potential Latency_95% Contrast P101
Visual Go/No Go Test Event Related Potentials_N2 Go Amplitude Task
Visual Go/No Go Test Event Related Potentials_N2 Go Latency Task
Visual Go/No Go Test Event Related Potentials_N2 No Go Amplitude Task
Visual Go/No Go Test Event Related Potentials_N2 No Go Latency Task
Visual Go/No Go Test Event Related Potentials_P3 Go Amplitude Task
Visual Go/No Go Test Event Related Potentials_P3 No Go Amplitude Task
Visual Go/No Go Test Event Related Potentials_Response Locked Correct Response Positivity [pc (Fcz] Task
Visual Go/No Go Test Event Related Potentials_Response Locked Error Positivity [pe (Cz)] Task
Visual Go/No Go Test Event Related Potentials_Response Locked Error Related Negativity [ern (Fcz)] Task
Visual Go/No Go Test_Mean Reaction Time Correct Go Trials Task
Visual Go/No Go Test_Mean Reaction Time Incorrect No Go Trials Task
Visual Go/No Go Test_Percent Correct Go Task
Visual Go/No Go Test_Percent Correct No Go Task
Visual Perception
Visuomotor Integration
Wechsler Intelligence Test For Children Revised Subtest_Block Design

Wechsler Intelligence Test For Children Revised Subtest_Digit Span
Wechsler Intelligence Test For Children Revised Subtest_Similarities
Wechsler Intelligence Test For Children_Arithmetic
Wechsler Intelligence Test For Children_Freedom From Distractibility
Wechsler Intelligence Test For Children_Full Scale IQ
Wechsler Intelligence Test For Children_Perceptual Organization
Wechsler Intelligence Test For Children_Performance IQ
Wechsler Intelligence Test For Children_Processing Speed
Wechsler Intelligence Test For Children_Verbal Comprehension
Wechsler Intelligence Test For Children_Verbal IQ
Wechsler Preschool and Primary Scale of Intelligence - Block Design
Wechsler Preschool and Primary Scale of Intelligence_Coding
Wechsler Preschool and Primary Scale of Intelligence_Composite Score
Wechsler Preschool and Primary Scale of Intelligence_Information
Wechsler Preschool and Primary Scale of Intelligence_Matrix Reasoning
Wechsler Preschool and Primary Scale of Intelligence_Picture Concept
Wechsler Preschool and Primary Scale of Intelligence_Symbol Search
Wechsler Preschool and Primary Scale of Intelligence_Vocabulary
Wechsler Preschool and Primary Scale of Intelligence_Word Reasoning
Wide Range Achievement Test_Arithmetic Score
Wide Range Achievement Test_Reading Score
Wide Range Achievement Test_Spelling Score
Wide Range Assessment of Memory and Learning_Learning Index
Wide Range Assessment of Memory and Learning_Verbal Memory Index
Wide Range Assessment of Memory and Learning_Visual Memory Index
Wisconsin Card Sort Test_Categories Competed
Wisconsin Card Sort Test_Perseverative Errors
Woodcock Reading Mastery Test_Passage Comprehension
Woodcock Reading Mastery Test_Reading Comprehension
Woodcock Reading Mastery Test_Word Comprehension
Woodcock-Johnson Tests of Achievement_Basic Reading
Woodcock-Johnson Tests of Achievement_Brief Reading

CURRICULUM VITAE
MICHAEL GOODMAN, MD, MPH

CONTACT INFORMATION

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EDUCATION

1995 M.P.H., THE JOHNS HOPKINS UNIVERSITY,
SCHOOL OF HYGIENE AND PUBLIC HEALTH
Baltimore, Maryland

1984 M.D., KAUNAS MEDICAL ACADEMY
Kaunas, Lithuania

POSTGRADUATE TRAINING

1994-1996 Residency in Preventive Medicine,
THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH
Baltimore, Maryland

1991-1994 Residency in Pediatrics
MONMOUTH MEDICAL CENTER
Long Branch, New Jersey

1988-1989 Fellowship in Academic Pediatrics
VILNIUS STATE UNIVERSITY HOSPITAL
Vilnius, Lithuania

1984-1985 Internship in General Pediatrics
VILNIUS STATE UNIVERSITY HOSPITAL
Vilnius, Lithuania

PROFESSIONAL EXPERIENCE

2017-present EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Department of Epidemiology, Atlanta, GA
Professor
Areas of research include transgender health, cancer epidemiology, global epidemiology of non-communicable diseases, cancer outcomes, children's health, and health disparities. Teaching assignments includes introductory course in epidemiology (4 credits, 170+ students) and a graduate seminar on

systematic reviews and meta-analyses (1 credit, 25-30 students). In addition, teaching responsibility include co-directorship of the dual degree MD/MPH program, offered jointly by Emory Schools of Medicine and Public Health.

2009-2017 EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Department of Epidemiology, Atlanta, GA
Associate Professor
Areas of research included cancer epidemiology, molecular epidemiology, cancer outcomes, children's health, and health disparities. Teaching assignments included introductory course in epidemiology (4 credits, 170+ students) and a PhD seminar on teaching epidemiology (1 credit, 7-8 students).

2003-2009 EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Department of Epidemiology, Atlanta, GA
Assistant Professor
Areas of research included cancer epidemiology, molecular/genetic epidemiology outcomes research, and children's health.

1996-2003 EXPONENT, Inc.
Health Group Washington, DC
Senior Managing Scientist
Designed and managed multiple projects including original epidemiological studies, scientific literature reviews, and meta-analyses.

1998-2003 BREAD FOR THE CITY CLINIC
Washington, DC
Pediatrician
Outpatient clinical care of pediatric patients

1994-1996 ST. AGNES HOSPITAL
PEDIATRIC EMERGENCY DEPARTMENT
Baltimore, Maryland
Pediatrician
Outpatient and emergency care of pediatric patients.

1995-1996 PANAMERICAN HEALTH ORGANIZATION
JAMAICAN OFFICE
Kingston, Jamaica
Consultant
Coordination of the Measles Immunization Campaign and implementation of the Polio Eradication Program

1994-1996 JOHNS HOPKINS UNIVERSITY MEDICAL CENTER
BAYVIEW CAMPUS
Baltimore, Maryland
Pediatrician
Outpatient, inpatient, and emergency care

1989-1990 AMERICAN JEWISH DISTRIBUTION COMMITTEE
Rome, Italy

Physician Assistant
Home visits and health monitoring of approximately 10,000 refugees during their temporary stay in Italy.

1985-1988 SHILALE COUNTY HOSPITAL
Shilale, Lithuania
Pediatrician
Outpatient and inpatient care in the department of pediatrics.

HONORS

1994 Martin Quirk Award Pediatric Resident of the Year, Monmouth Medical Center
2011 Student Government Association Professor of the Year, Rollins School of Public Health
2013 Excellence in Teaching Award, Department of Epidemiology, Rollins School of Public Health
2013 Emory Williams Distinguished Teaching Award, Emory University
2017 Phi Chapter of the Delta Omega Honor Society, Emory University

LICENSURE AND CERTIFICATION

American Board of Preventive Medicine Examinations, 1997, 2019
American Board of Pediatrics Examinations 1994, 1999
State of Maryland License D46297 (inactive)
District of Columbia Medical License MD000030144 (inactive)
State of Georgia Medical License 056716
National Provider Identifier 1710197520

PROFESSIONAL AFFILIATIONS (Past and Current)

American Academy of Pediatrics
American College of Epidemiology
American Association for Cancer Research
Endocrine Society
World Professional Association of Transgender Health
American College of Preventive Medicine

TEACHING EXPERIENCE (Current)

2009-present CENTERS FOR DISEASE CONTROL AND PREVENTION, EPIDEMIC INTELLIGENCE SERVICE (EIS)
Invited Faculty
Co-instructor for the *EIS Summer Course in Epidemiology*

2011-present EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH; EMORY SCHOOL OF MEDICINE JOINT MD/MPH PROGRAM
Program Director
Supervising MPH phase of the joint MD/MPH training program with 10-20 dual degree students annually

2011-present CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC UNIVERSITY)

Invited Faculty
Short course *Systematic Reviews and Meta-Analysis*

2015-present EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Instructor
Systematic Reviews and Meta-Analysis (20-30 students, 2 credits).

2018-present EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Instructor
Dual degree seminar (10-15 students, 1 credit).

2019-present EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Instructor
PhD seminar (10-15 students, 1 credit).

TEACHING EXPERIENCE (Past)

1993-1994 MONMOUTH MEDICAL CENTER
Long Branch, New Jersey
Chief-Resident in Pediatrics
Training and supervision of pediatric residents

1998-2003 JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH
Baltimore, Maryland
Preventive Medicine Rotation Supervisor at Exponent, Inc.
Epidemiology rotation preceptor for the Preventive Medicine Residency Program

2006 CAUCASUS REGIONAL CANCER CONTROL SUMMIT
Tbilisi, Republic of Georgia
Guest Lecturer
Cancer surveillance: Overview of goals, methods, and uses

2007 INDO-AMERICAN ONCOLOGY WORKSHOP
Ahmedabad, India
Guest Lecturer
Cancer incidence, mortality and survival: A US-India comparison

2012 NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO
Mexico City, Mexico
Guest Lecturer
Clinical trials of antioxidants: Past, present, and future
Use of biomarkers of oxidative stress in human research: example of colorectal neoplasia

2009-2011 MOREHOUSE UNIVERSITY SCHOOL OF MEDICINE, PREVENTIVE MEDICINE PROGRAM
Invited Faculty
Guest lecturer in Cancer Epidemiology for the Preventive Medicine residents

2011 PAN AMERICAN HEALTH ORGANIZATION (PAHO)
Invited Faculty
Co-instructor for the PAHO professional staff development course *Practice-based Epidemiology*

2006-2013 EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Instructor
PhD seminar: *Teaching epidemiology* (1 credit).

2014 SOCIETY OF TOXICOLOGY CONTINUOUS EDUCATION COURSE
Phoenix, AZ
Guest Lecturer
Epidemiology for toxicologists

2014 TEL AVIV UNIVERSITY
Invited Faculty
Co-teaching short course Advanced *Cancer Epidemiology*

2007-2014 NATIONAL CANCER INSTITUTE
Invited Faculty
Teaching module "Consideration for Analysis and Interpretation of Epidemiologic Data" in the NCI summer course *Principles and Practice of Cancer Prevention and Control*

2015 EMORY UNIVERSITY COLLEGE OF ARTS AND SCIENCES
Co-Instructor
Basic Epidemiology course (40 students, 1 credit).

2013-2016 EMORY PUBLIC HEALTH LEADERSHIP AND IMPLEMENTATION ACADEMY FOR NON COMMUNICABLE DISEASES
Guest Lecturer
Validity of Diagnostic and Screening Tests; Evaluation of Screening Programs

2006-2018 EMORY UNIVERSITY SCHOOL OF PUBLIC HEALTH
Instructor
Introduction to Epidemiology course (120-150 students, 4 credits).

UNIVERSITY SERVICE ACTIVITIES

2004-2005 Search committee for infectious disease epidemiology faculty
2004-2006 PhD Admissions Committee, Department of Epidemiology
2005-2006 Search Committee (chair) for new faculty
2005-2006 Emory/ACS Center for Global Cancer Control
2006-2008 Clinical and Translational Science Award (CTSA) Committee
2006-2010 Health Sciences Center Library Advisory Committee
2007-2010 Woodruff Fellowship Selection Committee
2010-2012 School of Public Health Re-accreditation Steering Committee
2012 Kennedy Survivorship Grant Review Committee
2006-2013 MPH thesis Shepard Award Committee

2014-2015	Search Committee for Director of English Language Support Programs
2011-2016	ARCS Foundation Award Committee
2015-2017	Emory University Conflict of Interest Committee
2007-present	MPH Admissions Committee, Department of Epidemiology
2012-present	School of Public Health Career Services Advisory Committee
2016-present.	Committee on English as Second Language at Emory
2017-present	Department of Epidemiology Curriculum Implementation Committee
2018-present	School of Public Health Re-accreditation Steering Committee

NATIONAL AND INTERNATIONAL SERVICE ACTIVITIES

2004-2006	Agency for Toxic Substances and Disease Registry (ATSDR) peer-reviewer
2008	National Cancer Institute, Scientific Review Group: Chemo-Dietary Prevention
2008	National Cancer Institute, Special Emphasis Panel/Scientific Review Group: The Cooperative Family Registry for Colorectal Cancer Studies
2009	Centers for Disease Control and Prevention Scientific review group: The *CDC Grants for Public Health Research Dissertation (R36)*
2010	Asthma UK Foundation grant review group
2011-2012	National Cancer Institute, Scientific Review Group: SELECT and PCPT Biospecimen Use
2012-2015	Vietnam Education Foundation application review group
2012	American University of Beirut multi-investigator grant reviewer
2014	World Cancer Research Fund grant reviewer
2015	Vanderbilt-Emory-Cornell-Duke Global Fellows Program application reviewer
2015	National Cancer Institute, Scientific Review Group: Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts
2018-	World Professional Association for Transgender Health Standards of Care Chapter Lead

SERVICE IN SCIENTIFIC JOURNALS

Associate Editor: Annals of Epidemiology (2008-2018)

Journal Reviewer: American Journal of Epidemiology; Annals of Epidemiology; BMJ Open; Breast Cancer Research; Cancer Epidemiology Biomarkers and Prevention; Clinical Cancer Research; Critical Reviews in Toxicology; Environmental Health Perspectives; European Journal of Cancer Prevention; International Journal of Epidemiology; Journal of Sexual Medicine; Journal of Toxicology and Environmental Health; Neurotoxicology; Nutrition and Cancer; Occupational and Environmental Medicine; Psychosomatic Medicine, PloS One, Transgender Health

RESEARCH SUPPORT (active projects)

AD-SS-4532 Patient Centered Outcomes Research Institute 01/01/19-03/31/20
Acute Thrombotic Events Following Feminizing Hormone Therapy
Annual direct cost: $264,640

The goal of this project is to characterize risk of venous thromboembolism and ischemic stroke in different subgroups of transfeminine people based on different characteristics of gender affirming hormone therapy they receive.
Role: Principal Investigator

EADI-12673 Patient Centered Outcomes Research Institute 01/01/19-03/31/20
Management of mental health problems among gender non-conforming youth
Annual direct cost: $213,309
The goal of this project is to educate health care providers (doctors and nurses), parents and school counselors about risks facing transgender children and adolescents, and to let them know about available ways of reducing these risks..
Role: Principal Investigator

R01CA230352 National Cancer Institute 4/1/19-3/31/24
10-year Comparative Effectiveness and Harms of Treatments for Prostate Cancer
Annual direct cost (subcontract): $62,745
The goal of this study is to provide information about long term outcomes of modern prostate cancer treatment modalities in a national cohort patients
Role: Site Principal Investigator (Atlanta site)

PC180927 Department of Defense 8/1/19-07/31/22
Racial Disparities in Active Surveillance Adherence and Quality of Life in a Population-Based Prospective Cohort of Men with Low-Risk Prostate Cancer
Annual direct cost (subcontract): $68,912
The goal of this study is to provide information about factors that affect adherence and outcomes of active surveillance as an initial management strategy for prostate cancer. .
Role: Site Principal Investigator (Atlanta site)

CFAR-03 National Institutes of Health Center for Aids Research 08/1/2019-07/31-2020
A Pilot Study of Transgender Health in the State of Tamil Nadu, India
Annual direct cost: $40,000
The overall goal of this study is to assess feasibility of a full scale cohort of transgender people in India, with specific focus on possible interaction between HIV status and use of cross-sex hormones.
Role: Principal Investigator

R01HD092595 National Institute of Child Health and Human Development 9/1/17-5/31/22
Pathways to care and health outcomes among DSD patients
Annual direct cost: $550,578
The goal of this project is to understand how patients with disorders of sex development (DSD) are treated and how they do later in life. This study, based on the national cohort of Kaiser Permanente enrollees, will likely be the largest study of DSD, and the first study of its kind in the United States.
Role: Principal Investigator

P20CA210298 National Cancer Institute 9/21/16-8/31/19
Planning a regional center of research excellence in non-communicable diseases in India
Annual direct cost: $289,628

The goal of this project is to combine data from four population-based cohorts and link these cohorts to existing cancer registries in India. This research infrastructure will be used to create a regional center of research excellence for non-communicable diseases.
Role: Principal Investigator

RSG CPPB124829 American Cancer Society 7/01/13-6/30/19
Why don't more men with low-risk prostate cancer choose active surveillance?
Annual direct cost (subcontract): $131,068
The goal of this proposal is to provide information about determinants of treatment decision in men with low-risk localized prostate cancer, particularly the factors that affect the offer, acceptance, and adherence of active surveillance as an initial management strategy.
Role: Site Principal Investigator (Atlanta site)

N01 PC35135 National Cancer Institute Renewable
Metropolitan Atlanta and Rural Georgia SEER Registry
Annual direct cost: $750,000
This is a population-based cancer registry covering 15 Georgia counties. It has been in operation since 1975.
Role: Medical director: (starting in April 2007)

R01 LM012372 National Library of Medicine 7/01/16-6/30/19
Novel Citation-based Search Method for Scientific Literature
Annual direct cost: $351,000
This project investigates whether efficiency of literature search can be improved without compromising sensitivity by systematically reviewing patterns and networks of studies that cross reference each other.
Role: Co-investigator

RESEARCH SUPPORT (completed projects)

AD-12-11-4532 Patient Centered Outcomes Research Institute 8/01/13-6/30/18
Annual direct cost: $569,476
Comparative risks and benefits of gender reassignment therapies
This project is used to assess clinical outcomes following various hormonal and surgical gender affirmation. This study is based on the national cohort of transgender individuals enrolled in the Kaiser Permanente health plan.
Role: Principal Investigator

CE-12-11-4667 Patient Centered Outcomes Research Institute 9/01/13-7/31/16
Annual direct cost (subcontract): $40,612
Generating critical patient-centered information for decision making in localized prostate cancer
Role: Site Principal Investigator (Atlanta site)
The goal of this proposal is to provide up-to-date data for treatment decisions in men localized prostate cancer by contacting patients 3-5 years after diagnosis.

1R01HS22640 Agency for Health Care Research and Quality 9/30/15-9/29/18
Annual direct cost (subcontract): $61,798
Comparative effectiveness of modern therapies for localized prostate cancer

The goal of this project is to provide up-to-date data for treatment decisions in men localized prostate cancer by contacting patients 3-5 years after diagnosis.
Role: Site Principal Investigator (Atlanta site)

R01CA98286 National Cancer Institute 8/01/2006-7/31/2016
Colorectal Chemoprevention with Calcium and Vitamin D
Annual direct costs: $250,000
This is a multicenter randomized, double-blind, placebo-controlled chemoprevention trial investigating whether supplementation with calcium carbonate and/or vitamin D will reduce recurrence of adenomas of the large bowel.
Role: Site Principal Investigator (Atlanta site)

R21HD076387 National Institute of Child Health and Human Development 8/01/13-7/31/16
Annual direct cost: 261,359
Cohort study of mortality and morbidity in transgender persons
The overall project goal is to assess the feasibility of a large-scale national prospective study of transgender individuals and will provide preliminary data on morbidity and mortality in this population.
Role: Principal Investigator

R01CA151736 National Cancer Institute 9/01/2010-2/29/2016
Effectiveness of Screening Colonoscopy in Reducing Deaths from Colorectal Cancer
Annual direct cost $80,000
The goal of this case-control study is to assess the effectiveness of screening colonoscopy in reducing death from colorectal cancer among average-risk adults when compared to no screening to evaluate the effectiveness of screening colonoscopy for reducing death from cancers of the right colon and left colon/rectum.
Role: Co-investigator

GR08657 Johnson and Johnson 8/01/13-5/31/15
Total direct cost: 115,355
Adverse effects of joint replacement among Kaiser Permanente Georgia patients
The overall project goal is to develop and pilot test a data collection protocol for a large-scale national study of arthroplasty patients.
Role: Principal Investigator

SIP-11-044 Centers for Disease Control and Prevention 9/30/11-9/29/14
Annual direct costs $500,000
State Registries as Platforms for High-Risk Cancer Screening
The primary goal of the study is to develop ways to improve screening and follow-up care for breast cancer in women and their first-degree relatives (mother, daughter, sister, half-sister) who may also be at increased risk for this disease.
Role: Co-Investigator

R21CA149350 National Cancer Institute 9/16/11-9/15/13
Annual direct costs $ 130,500
Mitochondrial Genetics in Prostate Cancer
The overall goal of this project is to determine the inherited mitochondrial DNA mutations in blacks and whites with prostate cancer by high-throughput DNA sequencing and to determine

drug sensitivity in cancer cells that harbor these mutations. Mutation-specific therapies will be explored.
Role: Co-investigator

R01 HS019356 Agency for Healthcare Research and Quality 9/01/10-8/31/13
Annual direct costs $ 1,466,582
Comparative Effectiveness of Treatments for Localized Prostate Cancer
This study compares the effectiveness of contemporary surgical and radiation techniques for localized prostate cancer in men at 6 and 12 months post therapy by evaluating patient-reported outcomes, side-effects, and complications associated with treatment.
Role: Site Principal Investigator (Atlanta site)

KPGA14470 Kaiser Permanente Georgia 5/01/2011-6/30/2013
Direct cost $80,000
Study of Race, Stress and Hypertension
The objective of this study is to provide pilot data for future research evaluating the genetic, phenotypic and environmental factors that may explain racial disparities in the prevalence and severity of hypertension. We will conduct a preliminary study designed to assess dietary, lifestyle and psychosocial exposures, in relation to blood pressure and presence of arterial hypertension in three groups of subjects: Caucasians, African-Americans and West African immigrants.
Role: Principal Investigator

UL1RR025008 National Institutes of Health 9/17/2007-5/31/2012
Atlanta Clinical and Translational Science Institute- Biostatistics and Epidemiology
Annual direct costs: $4,743,431
The Atlanta Clinical and Translational Science Institute (ACTSI) is an inter-institutional consortium that concentrates basic, translational, and clinical investigators, community clinicians, professional societies, and industry collaborators in clinical and translational research projects. The consortium of institutions includes Emory University, Morehouse School of Medicine and Georgia Institute of Technology.
Role: Co-investigator

DP09-0101Supp09-15 Centers for Disease Control and Prevention 9/30/2009-9/29/2011
Annual direct costs $500,000
Active Surveillance Attitudes and Perceptions in Prostate Cancer
The major goal of this proposal is to explore reasons why men and their significant others may select active surveillance as a treatment option in prostate cancer using a national sample of community centers, National Rural Health Association, and Veterans Affairs Medical Centers.
Role: Co-Investigator

R01 CA116795 National Cancer Institute 5/01/2007-4/30/2010
Oxidative Stress, DNA Repair & Colorectal Adenoma Risk
Annual direct costs: $250,000
The objective of the proposed study is to examine the associations among colorectal adenoma; determinants of oxidative stress, including dietary habits, biomarkers of oxidative damage, serum antioxidant levels; and genetic variation in antioxidant and DNA repair enzymes using data and biological specimens collected in a previous case-control study of incident, sporadic colorectal adenoma.
Role: Principal investigator

Winship Cancer Institute 10/01/2008-3/01/2010
Mitochondrial Factors and Prostate Cancer Risk in Whites and Blacks: A Pilot Population-Based Case-Control Study
Annual direct costs: $30,000
The objective of this study is to provide pilot data for future research evaluating the genetic, phenotypic and environmental determinants of oxidative stress as the underlying mechanism, which may explain the racial disparities in prostate cancer risk.
Role: Principal Investigator

R01 CA114524 National Cancer Institute 8/01/2007-7/31/2010
Race, Comorbidity & Long Term Prostate Cancer Outcomes
Total direct costs: $150,000
The goal of this proposed study is to better understand long-term (>10 year) health related quality of life in patients with prostate cancer.
Role: Site Principal investigator (Atlanta site)

N01-PC-95002-18-01 National Cancer Institute 8/01/2009-7/31/2010
Evaluation of Process Efficiency in the Task of Case Consolidation within SEER Registries
Total direct cost: $28,763
The goal of this study is to evaluate system-related process efficiencies in case consolidation, a routine task of central cancer registries. Recommendations will be made to optimize data management system design and improve operational efficiencies.
Role: Co-Investigator

N01-PC-95002-18-02 National Cancer Institute 8/01/2009-7/31/2010
Total direct cost: $ 47,889
Frequency and Predictors of Missing Data in Site-Specific Variables Recently Added to SEER
The objectives of the proposed study are to evaluate the completeness of the site specific variables recently added to SEER, to identify factors associated with missing information, and to quantify the resources required to collect these data.
Role: Principal Investigator

W18XWH-05-1 US Department of Defense 11/22/2004-11/21/2006
Total direct costs: $250,000
A VA Population Study of Disease Progression in Prostate Cancer Patients
This project examines the role of chromosome 8p deletion in modifying the value of clinical predictors of postoperative prostate cancer recurrence among US veterans.
Role: Co-investigator

U48DP00004301 Centers for Disease Control and Prevention 10/1/2004-9/30/2008
Total direct costs: $1,200,000
Treatment Decisions among Men with Localized Prostate Cancer in Southwest Georgia
This is a CDC-funded project to identify treatment options and factors influencing treatment decisions among men diagnosed as having prostate cancer in rural Georgia.
Role: Co-investigator

N01-PC-35135 National Cancer Institute 10/30/2004-7/1/2006
Assessment of Accuracy of Geocoding
Total direct costs: $150,000

This is a SEER rapid response surveillance study aimed at examining the variation and availability of address information in order to identify optimal methods of geocoding cancer registry data.
Role: Principal investigator

N01-PC- 32185 National Cancer Institute 9/30/2005-4/1/2007
Depth of Invasion for Tongue Cancer
Total direct costs: $20,000
This is a SEER rapid response surveillance study aimed at examining the variation and completeness of pathology information in surgically treated tongue cancers.
Role: Principal investigator

U48DP00004302 Centers for Disease Control and Prevention 10/1/2005-10/1/2008
Determinants of Patient Dropout from Cancer Treatment and Follow-up
Total direct costs: $300,000
This is a CDC-funded project that examines frequency and risk factors of failure to complete treatment among cases of prostate cancer, lung cancer, colorectal cancer, and breast cancer that reside and receive their treatment in rural Georgia
Role: Co-investigator

U01DP00025801 Centers for Disease Control and Prevention 10/1/2005-09/30/2008
Breast and Prostate Cancer Data Quality and Patterns of Care
Total direct costs: $900,000
This is a multicenter project that examines patterns of care among men with prostate cancer and women with breast cancer who reside and receive their treatment in the State of Georgia.
Role: Co-investigator

6-37249 Coca Cola Company 11/1/2005-03/1/2006
Study of the Association between Aspartame Consumption and Cancer in Humans: Feasibility Assessment
Total direct costs: $48,000
This study examined data availability and feasibility of an epidemiologic study of aspartame consumption and cancer in human beings by using data from one or more existing prospective cohort studies.
Role: Principal investigator

Woodruff Health Sciences Fund 9/30/2006-10/1/2008
Total direct costs: $128,000
Regulators and markers of oxidative stress in predicting and preventing prostate and colorectal neoplasms
This is a one-year project aimed at investigating new approaches for cancer risk prediction and prevention that uses existing samples from two previously conducted case-control studies. It takes into consideration inherent individual susceptibility and interactions among different factors that contribute to carcinogenesis via inflammation and oxidative stress pathways.
Role: Principal investigator

N01-PC- 32187 National Cancer Institute 9/30/2006-12/31/2008
Accuracy of biopsy-derived Gleason scores
Total direct costs: $70,000

This is a SEER rapid response surveillance study aimed at comparing Gleason scores assigned at diagnosis against those assigned by expert urologic pathologists specializing in this area.
Role: Principal investigator

RSG-05-038-01-CCE American Cancer Society 4/1/2005-3/31/2009
Measurements of Disease Progression in Patients with 8p Allelic Imbalance Prostate Tumors
Total direct costs: $600,000
This project examines the role of chromosome 8p deletion in modifying the value of positive surgical margin and Gleason score as predictors of postoperative prostate cancer recurrence.
Role: Co-investigator

PEER-REVIEWED PUBLICATIONS (229 total)
(*Asterisk indicates student projects)

Goodman, M., Lamm S, Engel A, Shepherd C, Houser O, Gomez M. Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. Journal *of Child Neurology,* 1997; 12(2): 85–90.

Jozwiak, S., **Goodman M**, Lamm S. Poor mental development in patients with tuberous sclerosis complex: clinical risk factors. *Archives of Neurology,* 1998; 55(3): 379–384.

Goodman, M, Lamm S, Bellman M. Temporal relationship modeling: DTP or DT immunizations and infantile spasms. *Vaccine,* 1998; 16(2–3): 225–231.

Hirshon J, Irons B, Figueroa P, Lewis-Bell K, **Goodman M**, Kirk G, Hersh B. Jamaica's measles elimination experience. *American Journal of Public Health,* 1999; 89(8): 1254-1255.

Goodman M, Morgan R, Ray R, Malloy C, Zhao K. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes and Control,* 1999; 10: 453-465

Goodman, M, Paustenbach D, Sipe K, Chapman P, Burke M, Figueroa R, Zhao K, Exuzides A. Epidemiologic study of pulmonary obstruction in workers occupationally exposed to ethyl- and methyl-cyanoacrylate. *Journal of Toxicology and Environmental Health Part A*, 2000; 59: 135-163.

Deubner D, **Goodman M**, Iannuzzi J. Variability, predictive value and uses of the beryllium lymphocyte proliferation test (BLPT): Preliminary analysis of the ongoing workforce survey. *Applied Occupational and Environmental Hygiene,* 2001; 16(5): 521

Goodman M, Kelsh M, Ebi K, Langholz, B, Iannuzzi J. Evaluation of potential confounders in planning a study of occupational magnetic field exposure and female breast cancer. *Epidemiology*, 2002; 13(1): 50-58.

Goodman M, Mandel J, LaVerda N, Clarke C, Iannuzzi J, Foster D. Neurobehavioral testing in workers occupationally exposed to lead: systematic review and meta-analysis of the published literature. *Occupational and Environmental Medicine,* 2002; 59: 217

Hessel P, Teta M, **Goodman M**, Lau E. Mesothelioma among brake mechanics: An expanded analysis of a case-control study. *Risk Analysis* 2004 24(3): 547-552

Goodman M, Teta MJ, Hessel P, Garabrant D, Craven V, Scrafford C, Kelsh M. Mesothelioma and lung cancer among motor vehicle mechanics: A meta-analysis. *Annals of Occupational Hygiene*, 2004; 48(4): 309-326

Mink P, **Goodman M**, Kelsh M, Barraj L, Yager J. Evaluation of uncontrolled confounding in studies of environmental exposures and neurobehavioral testing in children. *Epidemiology,* 2004; 15 (4): 385–393.

Zhou W, **Goodman M**, Lyles R, Lim S, Williams T, Rusthoven K, Mandel J, Amin M, Petros J Surgical margin and Gleason score as predictors of postoperative recurrence in prostate cancer with or without chromosome 8p allelic imbalance *The Prostate*, 2004; 61(1)

*Ludwig, M, **Goodman, M**, Miller, D, Johnstone P. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. *Chest*, 2005; 128 (3) 1545-1550

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